

PATHOLOGY IN SURGERY

BY

N CHANDLER FOOT, M D

*Professor of Surgical Pathology, Cornell University Medical College,
Surgical Pathologist, New York Hospital*

*368 Illustrations in Black and White and
20 Subjects in Full Color on 11 Plates*



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TO MY WIFE
IN GRATEFUL MEMORY OF
OUR DAUGHTER
ELLEN BELLOWS NEUMANN
(DR ELLEN B FOOT)

*A bright and witty spirit,
An accomplished and deft physician,
And an inspiration to all who knew her*

Preface

This book is intended as a guide to the surgical pathology of those disorders in which operations are carried out and organs or other specimens removed either as a remedial measure or for the specific purpose of obtaining biopsies leading to pathologic examination and diagnosis. For that reason it cannot be expected that we should explore those pathologic lesions that are seen only at autopsy, nor is it advisable that this book be too comprehensive in the theoretical consideration of all the aspects of the lesions that are described. It is intended that it should serve as a textbook for courses in surgical pathology per se and as a guide for physicians functioning in hospitals as surgical pathologists, men who have not had extensive experience in this subspecialty. It is essentially an expansion of the subject-matter of the Third-Year course in surgical pathology as it has been taught during the past twelve years in the Cornell University Medical College, but it will cover a far wider field than can be included in the time available for this purpose in a crowded curriculum.

The material that constitutes the basis for the study of this subject falls into four categories: (A) Trauma, (B) developmental anomalies, (C) inflammatory lesions, and (D) tumors. The order of presentation of these categories is roughly in accordance with their comparative importance, with the least important given first. Traumatic lesions are usually fully recognized and understood by the surgeon, and such material, when sent to the laboratory, requires little more than a cursory inspection and a brief gross description. Embryologic rests and malformations, such as branchiogenic cysts, Meckel's diverticula, supernumerary ear buds and digits, pilonidal sinuses, and the like may or may not

require careful examination from both gross and microscopic standpoints. Inflammatory lesions are very common, and those of the appendix and gallbladder constitute the vast majority of specimens submitted for examination, less numerous are gastric and intestinal lesions, while among the rare examples are biopsies of dermal lesions, lesions of lymph nodes, and similar types of material. Although tumors may not be as numerous as inflammatory lesions in the day's routine, they constitute the most important group of specimens because of the necessity of diagnosing them as noncancerous or cancerous lesions and of prognosing the possibility of their eradication by a specific operative procedure.

It will be well, therefore, when we come to the consideration of the subject matter of surgical pathology, to arrange it accordingly, with general discussions of the nature of these lesions and an adherence to the order of their importance when taking up the more specialized descriptions of pathologic conditions of the various systems of the human body.

So far as the various systems of the human body are concerned, it may seem on casual inspection, that undue emphasis has been placed upon certain tracts while others have been neglected. A moment's thought will explain the reasons for this. Most of the major operations in a general hospital are carried out upon the alimentary tract, the breast and the genito-urinary system, therefore there is ample need for reference to these and the chapters dealing with them are necessarily fuller and longer than those that are concerned, let us say, with the respiratory tract or the muscular system.

Another reason for expanding certain sections of the book at the expense of others is that data on surgical material from the

erous system or skin, for example, are not readily available or assembled in books such as this one. The pathology of the skin is largely presented in special volumes on dermatology or dermatologic pathology, and yet biopsies of the human integument are very numerous in many hospitals where the dermatologists are interested in knowing more than the mere clinical features of their cases.

This has been largely a "one-man book" and the writer accordingly assumes responsibility for the opinions it sets forth. He was, however, been assisted by a number of colleagues to whom his warm appreciation is due. The entire manuscript was read in its preliminary draft by Dr. Charles Neumann, who made many valuable suggestions that were promptly adopted by the writer and found to be of distinct assistance. Dr. George Labalme was a great help in having catalogued and briefly described much of the interesting material in the departmental collection of slides. Thus, when it became necessary to select sections for photomicrographs he was able to put his finger on the required material and thus saved the writer much time and labor. Most of the photomicrographic illustrations were taken by Mr. Robert Waldeck of the Department of Photographic Illustration of the Cornell University Medical College. Owing to his

exact methods and uniformity of procedure these pictures have been correspondingly uniform and eminently satisfactory. Colonel Frederick H. Foucar of the Second Service Command Laboratory of the United States Army very kindly loaned the illustrations credited to him and to the Army Medical Museum. Miss Elizabeth Brödel gave kindly and profitable advice and criticism in connection with the drawing of the colored illustrations.

After employing Dr. Howard T. Karsner's "Human Pathology" as a model upon which to erect the structure of this book, the author was extremely pleased and grateful when Dr. Karsner proposed that it be published in a format uniform with that of his text-book, as a sort of ancillary volume. Many of the references at the end of each chapter of this book were taken from Dr. Karsner's volume. The writer is also indebted to the personnel of his department for their coöperation in preparing special sections for illustrations. He is very appreciative of the courtesy and efficiency of his publishers in getting the manuscript into print, as well as grateful for their exceptionally friendly and helpful relations with him during its preparation.

To all these good friends many thanks!

N. C. F.

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1

Field, Procedures, and Technics of Surgical Pathology

RELATION OF SURGICAL TO GENERAL PATHOLOGY
DUTIES OF THE SURGICAL PATHOLOGIST
DEPARTMENTAL PROCEDURE
SPECIMENS
RECORDS
PERSONNEL
LABORATORY METHODS
GROSS EXAMINATION

LABORATORY METHODS (*Continued*)
FIXATION
EMBEDDING
SECTIONING
STAINING
SILVER IMPREGNATIONS
ELASTIC-TISSUE STAINS
STAINING MICRO ORGANISMS IN TISSUE

RELATION OF SURGICAL PA- THOLOGY TO GENERAL PATHOLOGY

Surgical pathology is a specialized branch of general pathology which has become more or less divorced from the latter and has been taken over by the surgeons, in some institutions, because they have definite needs and have found that the average department of pathology assigns this important work to one of its junior members, usually a resident, who necessarily lacks the clinical and pathologic experience essential for rapid and authoritative diagnoses. Busied with the routine of necropsies, teaching, and research which can ill afford interruption, the senior pathologists are apt to regard surgical pathology as a minor branch of rather secondary importance in their field of endeavor. As a result of this, many surgeons have taken over this routine themselves, or have employed pathologists to give their full time to surgical specimens, thus not only insuring prompt reports on specimens but also the undivided attention of the incumbent who is at all times at their disposal for carrying out frozen section diagnoses, for advice in the operating room

while the patient is on the table, or for consultations concerning their difficult cases. The last two of these functions are of a sort that may not be entrusted to any but an experienced pathologist. That the surgical pathologist should be first a surgeon and only incidentally a pathologist is not a good idea at all, as it is essential that he should have had extensive training and experience in general pathology and its methods before he can acquire the proper perspective. If he have a working knowledge of surgery as well, this is all to the good, for he can then combine this with his experience in pathology in connection with his advice as to the future treatment of a case that entails a choice of surgical procedures.

Although surgical pathology may be a branch of general pathology as considered from the academic viewpoint and would appear to comprise elements of knowledge and experience that would presumably be familiar to the general pathologist, this is not entirely the case. Any general pathologist undertaking the practice of this sub-specialty will soon discover that he is dealing with conditions rarely studied in the laboratory of general pathology. There is

a mass of small things in the day's routine of any surgical pathologist that would not interest anyone doing a necropsy upon a patient dead of some interesting and important malady; these are of distinct interest to the surgeon in the dispensary who is performing diagnostic biopsies and removing small moles, sebaceous cysts, bits of tendon and tendon-sheath, and like specimens concerning the nature of which he is curious and about which he must have information. Among these one frequently encounters important and often puzzling specimens.

This subspecialty differs radically from its parent specialty, general pathology, in one important particular: it deals with the future rather than with the past. It is not so much a question as to what was wrong with the patient as it is one of prognosis as to what will probably happen to him in the future as a result of a given lesion. Concerned with a tumor, for example, the surgeon may be interested in the diagnosis, but he is sure to wish to know whether the growth will recur, or metastasize, or respond to irradiation, and, further, if it has apparently been totally removed. These and many other questions confront the surgical pathologist and constitute the subject of consultation with the surgeon who usually places implicit faith in his dicta. Thus much depends upon such decisions

DUTIES OF THE SURGICAL PATHOLOGIST

The duties of a surgical pathologist, then, vary with a given case: he may be required to make a diagnosis by a macroscopic examination of the lesion in situ while the patient is on the operating table and the operation in progress: it may be necessary for him to make a microscopic examination by rapid methods while the operation goes on, in order to determine what should be the further procedure of the surgeon. In many hospitals it is the rule for the surgical pathologist to examine all material, however trivial, that is re-

moved by operative measures. This is a wise precaution, as it safeguards both surgeon and hospital in case of doubt as to what was or was not removed at operation and protects them in the case of lawsuits for damages. It is not necessary that every specimen should be described and examined microscopically; many of them (such as hernial sacs, hypertrophic tonsils, varicose veins, and the like) may be subjected to a rapid but thorough scrutiny and then listed as "inspected but not described." In the course of such examinations it sometimes happens that important lesions are detected and then examined microscopically—lesions that would have been overlooked had the specimen been simply discarded in the operating room.

Other specimens require careful macroscopic and microscopic examination and constitute the bulk of the laboratory routine. Aside from operative material there are always a number of diagnostic biopsies from various clinics in the hospital. The dermatologists excise portions of skin-eruptions, the bronchoscopists send in material removed in the course of bronchoscopy or esophagoscopy. Biopsies from the urinary bladder and the lower intestinal tract are numerous. The hematologists send in bits of cancellous bone from the sternum for examination of the marrow; the internists submit aspirated fluids from the pleural and peritoneal cavities, possibly from the pericardium, for sedimentation and "cell blocks"; and the gynecologists wish microscopic examination and diagnosis of uterine curettings and pieces of tissue spontaneously passed. Thus the diagnostic work covers a wide variety of pathologic conditions which may even include those of the eye. All this requires a broad grasp of pathology, including that of systems not frequently invaded by the general pathologist, either because the lesions are too trivial as compared with lethal ones that have made a necropsy desirable or mandatory, or because of ethical or legal restrictions that often preclude the re-

removal of interesting superficial lesions that might lead to disfigurement of the subject

DEPARTMENTAL PROCEDURE

A prime factor in the success or failure of a department of surgical pathology is the time element, surgeons cannot and will not wait weeks or even days for a diagnosis of their pathologic specimens, and it is this factor that has forced them to attempt to administer their own pathologic investigations. For this reason every attempt should be made to submit prompt reports on surgical material, which is not at all difficult if the departmental chief sees to it that this is run through rapidly, examined promptly, and reported upon without delay.

Specimen Blanks Each specimen submitted to the laboratory should be accompanied by a slip filled out with the patient's name, age, history number, and ward or room number. The name of the operating surgeon should also be given, and a space should be provided for the laboratory serial number when this has been assigned to the specimen. There should be lines for the clinical and operative diagnoses and several for the jotting down of a few essential clinical data. Then the surgical pathologist, when he receives the specimen, will know something about the patient.

Submittal of Specimens Specimens of any appreciable bulk should be wrapped in gauze moistened with saline solution and this should in turn be enclosed in waxed paper and accompanied by a small label with the patient's name, age, history number, ward, and the name of the operator. Without such an attached label the slip (which is usually filled out by an intern or resident) may become separated from the parcel, which is then difficult to identify. One thus has a double check upon each specimen.

Records The descriptions of the gross material are dictated to a stenographer or into a dictaphone and later typed onto

sheets, at least two carbon copies should be made on plain serviceable paper while the original is typed on a special sheet or form that becomes a part of the patient's hospital record. One of the carbon copies is then filed alphabetically under the patient's name and the other in a numerical series according to the laboratory serial number. It is also well to enter all material under serial numbers in a daybook which has columns for the numbers, the patient's name, history number, ward, nature of the material, the name of the operating surgeon, and the diagnosis. In this book all "inspected" specimens should also be entered. In this way a given specimen may always be located with reasonable ease, if one has the name, or the laboratory number, or the daybook entry to which one may refer.

A convenient method for numbering specimens is one that was originated by Frank Mallory. One starts on January 1st with the last two digits of the year (say 45) and appends to this the number of the specimen (say 123). In a department of general pathology the autopsy material may be numbered with an initial "A" or "N" (for "necropsy"), the surgical material with "S," and the private or "outside" material with "P." At the end of the year the accumulated records, alphabetically arranged, are pooled and alphabetically incorporated with those of previous years in a large filing cabinet, while the numerical files may remain undisturbed and kept as annual series. The reason for this is that when a physician wishes to refer to a record or a section he usually knows the name and history number of his patient, although he may be rather hazy as to when that patient was in the hospital and is seldom familiar with the laboratory number assigned. One cannot use history numbers for filing, as they do not run consecutively, only a certain percentage of patients being admitted to the surgical service. It has been found by experience that the pooled back-record method seldom fails one.

To illustrate a physician wishes to see the record or examine the microscopic sec-

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tion of a certain Jane McDavitt; looking up this name under the "Mc's" one finds several reports covering as many years; each one bears a laboratory number (say S 41 5115, S 32 106, and S 21 27), so that the sections may then be extracted from the slide cabinets and the physician not only may have the specimen he requested but may discover others that have a definite bearing upon his patient's case and concerning the existence of which he had no knowledge. The type of numbering recommended indicates the year in which the patient was operated upon and the approximate month in that year; it also prevents the accumulation of digits in the laboratory numbers to a point where they become cumbersome and difficult to decipher. The average large general hospital will have from 5,000 to 10,000 surgical specimens per annum, so that mere consecutive numbers soon become confusingly bulky.

Personnel. The surgical pathologist should have at least one assistant who is preferably recruited from the resident staff of the hospital; a surgical resident makes a valuable assistant, once he has been trained, as he is in touch with the surgical service and knows something about the histories of the patients undergoing treatment. It is invaluable training for a surgeon to have served a turn in the laboratory, for his ability to distinguish pathologic from non-pathologic conditions encountered in his future surgical practice will depend largely upon this training.

One or more "tissue technicians" are a *sine qua non*, preferably women who have had training in a laboratory of general pathology or histology and who have had college educations with some experience in biology. One may train a high-school graduate satisfactorily, but it is always better to have a technician who knows something about histology and has a background of some laboratory instruction. It is necessary to have a stenographer who can take care of the typing of the records and of the reference files of reports. She can often answer

questions from the wards as to diagnoses and save the time of the pathologist and his assistant.

LABORATORY METHODS

Gross Examination of Specimens. All specimens should be carefully examined with the naked eye, and if important should be measured, weighed, and described. Small specimens like appendices and gallbladders need not be weighed, but thyroids, kidneys, and the like, as well as prostates or masses of prostatic fragments from transurethral resections, should always be accurately weighed. Such descriptions often are a matter of routine and quite without interest, but they document the case and may prove to be invaluable in the event of lawsuits or as indications to surgeons, who may treat the patients later, of what was done at previous operations.

From those specimens that are deemed worthy of microscopic examination, blocks should be cut with a sharp knife; these should never exceed 4 mm. in thickness, although their area may be as extensive as is practical. In cutting blocks from a specimen it is absolutely necessary to use selective judgment; any convenient part of the specimen will not suffice. After the tissue has been inspected those areas that give the most promise of affording good histologic material and that show the most characteristic gross lesions should be chosen. Never cut blocks from necrotic foci, as so often is done in the case of tumors; it is sheer waste of time.

When descriptions are dictated into a dictaphone it is best to have the machine fitted with a foot switch to prevent contamination of the apparatus with blood or other dirty matter.

FIXING PATHOLOGIC MATERIAL

There are many fixing fluids, but it will be necessary to consider only the more valuable members of the group which may be used as a routine measure.

Neutral Aqueous Formalin This is an aqueous solution of formaldehyde in water (40 per cent) that is usually used in a dilution of one part in ten of water and known as "10 per cent formalin." One should put an excess of marble in the shape of chips in the stock solution so as to counteract the formic acid that would otherwise form. The chips should not be allowed to crumble, if they do, fresh chips should be added. Tissue fixed for 10 to 24 hours may be used for immediate sectioning, but if the blocks are to be kept in the wet state for some time it is better to transfer them to 80 per cent alcohol after a few days in the formalin. Formalin is an excellent fixative, but it has its limitations, particularly in connection with aniline dyes and with the Masson trichrome technic, in both of which this fixation fails to give satisfactory results.

Alcohol formalin In the routine of the laboratory this makes an excellent all-around fixing fluid. It is made up of 10 parts of concentrated 40 per cent aqueous formaldehyde in 90 parts of 95 per cent alcohol. It has the advantage of dehydrating while it fixes, and it may be used in connection with the Masson trichrome stain if one make certain concessions regarding the depth of the red elements in the resulting color scheme, as these may be rather pale at times. Alcohol alone is apt to cause noticeable shrinkage of the tissue, but when combined with formalin its percentage is reduced to a point where there is minimal shrinkage, certainly no more than one observes in the case of neutral 10 per cent formalin. This fixative cannot be used with aniline dyes which demand chromium salts as mordants in the fixing solution. After ten years' use of alcohol formalin we still find it the best for all rapid work and a shortener of the time necessary for preparing sections and rendering reports on the resulting examination.

Absolute Alcohol This tends to shrink tissue to an undue extent, but it is imperative to use it as a fixative if one desires to examine tissue for glycogen, which is very

soluble in water, a situation in which aqueous fixing solutions are strictly contraindicated.

Zenker's Fluid This is a combination of potassium bichromate and mercuric chloride, with acetic acid added just before use. Once the acid has been added, the solution will deteriorate if allowed to stand more than a day or so. The stock solution is made up as follows:

Potassium bichromate	2.5 Gm
Mercuric chloride	8.0 Gm
Water	100.0 cc

The mercuric chloride should be dissolved in hot water before adding to the mixture, the water used being subtracted from the total of 100 cc. This stock solution is technically "Muller's solution," and the addition of 5 cc of glacial acetic acid just before use makes it "Zenker's." The stock Muller's solution is conveniently made up in 4 liter lots and stored in large bottles. Zenker fixed material must be washed in running water for at least ten hours before the tissue is embedded, it is completely fixed in about ten hours. As this fixation leaves crystals of mercuric chloride in the tissue, this should always be removed from the sections before they are stained. This is accomplished by immersion in Lugol's I.K.I. solution or a light brown alcoholic solution of iodine for several minutes, next bleaching the browned sections by a short bath in 0.5 per cent aqueous sodium thiosulfate ("hypo"). This is an important procedure as the mercuric chloride crystals are very disturbing and their presence precludes decent photomicrographs. Zenker's fluid is one of our best fixatives, being an excellent mordant for any subsequent aniline dyes and affording unsurpassed nuclear detail, but it tends to render the tissue hard and brittle and may be troublesome on that account, particularly in connection with inherently tough tissues like skin and fibrous tumors.

Bowen's Solution This is a very excellent fixative when one desires to obtain

brilliant color reactions and a minimum of hardening and shrinkage. The following formula, substituting trichloroacetic acid for the usual acetic acid, has been found to be particularly satisfactory:

Formalin (concentrated)	100 cc.
Trichloroacetic acid 2%	20 cc.
Picric acid to saturation	
Water	300 cc.

This, too, is conveniently made up in lots of a gallon or 4 liters. It is especially suited for the fixation of dermal biopsies which become brittle and hard to section when fixed in other solutions.

Cajal's "Bromformol" Fixative. This is excellent as a preliminary to silver impregnations of neuroglia when it is desirable to enhance the impregnation of neuroglial fibers and to suppress that of the reticulum. Devised by Ramon y Cajal and extensively used by Hortega, it is made up as follows:

Ammonium bromide	3.0 Gm.
Concentrated formalin (neutral)	15.0 cc.
Water to make	100.0 cc.

Chloral Hydrate. This is used in a 25 per cent aqueous solution as a fixative for sections of central nervous system in which one desires to impregnate with silver the nerve endings, axones of ganglion cells, axis cylinders of peripheral nerves and non-medullated nerves. Without its use impregnations are capricious and apt to be very uneven.

General Remarks on Use of Fixatives. In practice one fixes all specimens in formalin alcohol for rapid results; some of them, of a more important and unusual type (tumors, material for photomicrography, etc.), should also be fixed in Zenker's and Bouin's fluids; those that consist of nervous tissue, or in which one wishes to demonstrate this, should be fixed in all the fluids just enumerated and described excepting absolute alcohol. It is depressing when one discovers that a given tumor which was thought to be muscular or glandular, turns

out to be composed of nervous tissue and one has no properly fixed material on hand with which to carry out special stains. There are a number of makeshifts, such as "bromurating" sections or "Zenkerizing" them in the paraffin oven, but these methods are never very satisfactory. If tissue is fixed in alcohol-formalin, Zenker's and Bouin's fluids simultaneously, one then has a scale of varying stains and histologic pictures from which to work, as each fluid affects different tissue elements somewhat differently. With the Masson technic alcohol-formalin fixation results in rather delicate and lightly colored effects; Zenker's fluid is unrivalled for sharp detail, resembling a steel engraving in its clarity of line; Bouin's solution results in brilliant color effects and contrasts. Thus one has not one rendition of a given section, but three of them that vary and from which one obtains a much clearer composite idea of the true morphology of the tissue examined.

EMBEDDING

After fixation the tissues are ready for embedding in paraffin; the process that they undergo is essentially dehydration, although further fixation and mordanting may be brought about at the same time, since alcohol is a coagulant and dioxane (should it be used) has a mordanting as well as a dehydrating and coagulating effect. Tissue blocks may be embedded by hand, or in the Autotechnicon, a machine that accomplishes the process overnight.

There are many methods for embedding tissue, but the surgical pathologist is chiefly interested in those that take the shortest time compatible with satisfactory results. For routine use an excellent method is listed as No. 2 by Mallory. The steps are as follows:

1. 95% alcohol (2 changes) 6-24 hrs. incl.
2. Absolute alcohol
(2 changes) 6-24 hrs. incl.
3. Chloroform 6-24 hrs.

- 4 Chloroform saturated with paraffin 6-24 hrs
- 5 Paraffin bath (hot, 2 changes) 2-4 hrs incl
- 6 Block in paper or tin pans and cool quickly in ice water

In using this method one should arrange the time factors so that the material may be changed during the day and left over night in those fluids which cause the least hardening, absolute alcohol and hot paraffin should be regarded as the most harmful in this respect

Dioxane Hand Method A very simple and satisfactory method has been devised by Graupner and Weissberger, utilizing dioxane which is an ether that is miscible with both paraffin and water and exerts considerable mordanting effect. It is carried out as follows

- 1 Dioxane, 100% 1 hr
- 2 Dioxane, 100% 1 hr
- 3 Dioxane, 100% 2 hrs
- 4 Hot paraffin bath 15 min
- 5 Same 45 min
- 6 Same 2 hrs
- 7 Block and chill in ice water

The repetitions in this method refer, of course, to changes to fresh solutions. The dioxane takes up water and the paraffin will at first contain dioxane, both of these must be eliminated. Dioxane may be used over and over again for some time if it be kept free of water by the addition of a little calcium chloride or calcium oxide, in which case there should be a wire screen raised a few millimeters above the bottom of the beaker so as to prevent the blocks of tissue from resting directly upon the calcium salts. Poisoning from the fumes of dioxane has been reported, but in a well ventilated laboratory it has never caused any symptoms among our technicians after seven years of use as an embedding agent.

There are other short methods for rapid embedding which may be found described in any good handbook of microscopic tech-

nic. They are usually not to be recommended, however, as they cause a great deal of shrinkage and distortion, it is far better to depend upon frozen sections for rapid diagnosis.

Embedding in the Autotechnicon This machine reduces the time of embedding and has been found to be an indispensable adjunct in the laboratory, as it is possible to charge it with blocks of tissue at 5 P.M. and to have them impregnated with paraffin at 9 A.M. on the following day. Blocks are placed in small perforated "cassettes" with snap covers, and these are in turn put into a perforated metal basket that is suspended from an arm of the machine and alternately lowered into and raised out of a succession of beakers containing dehydrating fluids until a paraffin container is reached. This is automatically and electrically heated to and kept at the desired temperature, as is the preceding container which is filled with dioxane and paraffin. The machine is actuated by an electric clock with a rotating cardboard fiber dial that is notched at the desired intervals to trip the switch that puts the motor in motion. The notches thus start and stop the rotating machinery and change the blocks from beaker to beaker as predetermined by the technician.

There are many schedules in use in connection with this apparatus, that given below has served us well for many years and was worked out by trial and error.

- 1 Alcohol formalin, 10% 6 hrs
- 2 Dioxane, 100% 1 hr
- 3 Dioxane, 100% 2 hrs
- 4 Dioxane, 100% 1 hr
- 5 Dioxane paraffin (sat sol at 42° C) 4 hrs
- 6 Paraffin at 56° C 4 hrs
- 7 Paraffin at 56° C in paraffin oven and off the machine 1 hr
- 8 Block and chill rapidly in ice water

Zenker or Bouin fixed material may be run through with the day's routine after suitable washing, the fact that it will stay in alcohol formalin for 6 hours seems to

brilliant color reactions and a minimum of hardening and shrinkage. The following formula, substituting trichloroacetic acid for the usual acetic acid, has been found to be particularly satisfactory:

Formalin (concentrated)	100 cc.
Trichloroacetic acid 2%	20 cc.
Picric acid to saturation	
Water	300 cc.

This, too, is conveniently made up in lots of a gallon or 4 liters. It is especially suited for the fixation of dermal biopsies which become brittle and hard to section when fixed in other solutions.

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out to be composed of nervous tissue and one has no properly fixed material on hand with which to carry out special stains. There are a number of makeshifts, such as "bromurating" sections or "Zenkerizing" them in the paraffin oven, but these methods are never very satisfactory. If tissue is fixed in alcohol-formalin, Zenker's and Bouin's fluids simultaneously, one then has a scale of varying stains and histologic pictures from which to work, as each fluid affects different tissue elements somewhat differently. With the Masson technic alcohol-formalin fixation results in rather delicate and lightly colored effects; Zenker's fluid is unrivalled for sharp detail, resembling a steel engraving in its clarity of line; Bouin's solution results in brilliant color effects and contrasts. Thus one has not one rendition of a given section, but three of them that vary and from which one obtains a much clearer composite idea of the true morphology of the tissue examined.

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After fixation the tissues are ready for embedding in paraffin; the process that they undergo is essentially dehydration, although further fixation and mordanting may be brought about at the same time, since alcohol is a coagulant and dioxane (should it be used) has a mordanting as well as a dehydrating and coagulating effect. Tissue blocks may be embedded by hand, or in the Auto-technicon, a machine that accomplishes the process overnight.

There are many methods for embedding tissue, but the surgical pathologist is chiefly interested in those that take the shortest time compatible with satisfactory results. For routine use an excellent method is listed as No. 2 by Mallory. The steps are as follows:

1. 95% alcohol (2 changes) 6-24 hrs. incl.
2. Absolute alcohol
(2 changes) 6-24 hrs. incl.
3. Chloroform 6-24 hrs.

bringing it to a boil, sections are then cut on the freezing microtome and floated on cold water, from which they are picked up on slides smeared with the albumen glycerol adhesive. They are then blotted dry with at least four layers of "bibulous paper," which is finer than filter paper and does not leave the marks of its weave on the blotted section. The section is then firmly attached to the slide by flooding it with 95 per cent alcohol from a dropping bottle, next with 100 per cent alcohol, and then following this with a few drops of celloidin dissolved in alcohol and ether and so diluting it that it is water thin. After dropping on the celloidin the slide should be quickly turned on its side so that the celloidin may run off and leave a very thin film. One then reverses the alcohol treatment, flooding with 100 per cent alcohol, then 95 per cent, and then placing the slide in water until it is to be stained. This method is admittedly longer and more complicated than that employing fresh, unfixed tissue, but the results are comparable with paraffin sections and can, if necessary, be saved as permanent records. This is often necessary when there has been too little tissue submitted to afford both frozen and paraffin sections and the surgeon has desired a frozen section diagnosis. Frozen sections may be stained in any way that paraffin sections can, hematoxylin and eosin stains are usually employed as simplest and most reliable.

Staining Sections. As this is not a manual of stain technology only a few methods will be described, but it is believed that they cover the requirements demanded by the routine of surgical pathology.

HEMATOXYLIN EOSIN STAIN. The simplest, most fool proof and reliable staining method is the hematoxylin eosin stain, for which two solutions are needed: a good preparation of hematoxylin and a water soluble yellowish eosin solution. Of the various hematoxylin formulae that of Harris has proved itself to be very valuable, it is easy to make up, it keeps well, and it gives a good stain. It is prepared as follows:

Hematoxylin crystals	1 0 Gm
Absolute alcohol	10 0 cc
Ammonium or potassium alum	20 0 Gm
Distilled water	200 0 cc
Mercuric oxide	0 5 Gm

The hematoxylin is dissolved in the alcohol and the alum in the distilled water with the aid of heat. The two solutions are then mixed and brought to a boil as rapidly as possible, whereupon the mercuric oxide is added. As soon as the mixture is a rich purple it is removed from the flame and cooled by plunging the container into cold water. It is always well to add 8 cc of glacial acetic acid if sharp nuclear detail is desired.

EOSIN. A saturated aqueous solution of eosin Y (water soluble) should be made up as stock and diluted to the required percentage. If the user prefers delicate eosin staining the concentrated solution, which is about 44 2 per cent eosin, should be diluted to make a 0 5 to 1 0 per cent solution, if he prefers deep red effects a 2 to 5 per cent solution may be used, but exposure to these strong solutions must be measured in seconds when staining sections. One should always add to the desired solution 25 per cent of alcohol to prevent deterioration.

The stain is carried out by placing sections in the hematoxylin from one to five minutes according to its freshness, older solutions becoming weaker through dilution. The sections should then be well soaked in water and, if very precise nuclear details are desired, differentiated in 1 per cent hydrochloric acid until reddish clouds come off the sections. They are then either washed several minutes in water or blued by exposure to water into which a few drops of strong ammonia have been introduced. The eosin stain then follows. Weak solutions require about five minutes, if 5 per cent solutions are used they should be poured on and off almost immediately, with a rinse in water to follow. The sections may stand in this water for a while. They are then dehydrated in ascending percentages

make no difference. Zenker-fixed material should be washed for 10 to 24 hours in running water, Bouin-fixed tissue is first washed in successive changes of 50 per cent alcohol until the latter no longer becomes yellow; it is then dehydrated and infiltrated as above. There are many ways, other than embedding tissue, of using this versatile machine. It may be employed in staining sections and in other ways described in a booklet issued by the manufacturer. The later models are fitted with a washing chamber, so that Zenker-fixed material may be washed, dehydrated, and infiltrated mechanically. When Sundays or holidays intervene, several beakers filled with 80 per cent alcohol may be interposed between the formalin-alcohol and the dioxane beakers and the machine may be set for a 48-hour cycle. Thus, tissue placed in the first beaker on Saturday afternoon will be embedded and ready for final embedding and sectioning by Monday morning.

SECTIONING

Paraffin sections are best cut at approximately 5 to 8 microns on a rotary microtome, by which ribbons are produced, each section adhering to its predecessor. These are then floated on water just hot enough to flatten them out and remove any wrinkles, but not hot enough to melt the paraffin. A Pyrex pie plate on an electric hot-plate with three intensities of heat is a very convenient setup for this purpose. One or more sections may then be cut from the ribbons by means of a heated scalpel and floated onto microscopic slides that have been previously smeared with an adhesive such as Mayer's or Spoerri's (described below). Either of these may be recommended.

Mayer's albumin-glycerol is composed of equal parts of the white of a fresh-laid egg and glycerol thoroughly beaten up and filtered through absorbent cotton or filter paper at a temperature of 54° C. A small lump of thymol should be added to prevent decomposition.

Spoerri's starch paste consists of 1 Gm. of powdered starch added to 10 cc. of cold water. These are thoroughly mixed and the solution poured into 20 cc. of boiling water. Two drops of dilute hydrochloric acid are added and the suspension is boiled and stirred for five minutes. A small crystal of thymol is added when the mixture has cooled.

Either of these adhesives may be spread out thin on a microscopic slide, the side of the hand being used as a squeegee. The starch paste has the advantage of being readily procurable, whereas it is often difficult to get fresh eggs. It should be remembered that sections will often adhere to clean slides by simple capillary attraction, no paste being necessary. When the paraffin sections are mounted on the glass they are dried in place by the application of gentle heat, such as may be best obtained in a drying-oven at 60°. Heating on an electric hot-plate is possible and feasible, but one must guard against overheating, which will ruin the staining property of the sections. After the slides have been dried and passed through xylol, absolute alcohol, and 95 per cent alcohol they are transferred to tap water and are ready to stain. The slides are best handled in glass boxes that hold ten of them at a time; the dehydration or hydration is thus readily carried out by pouring the solutions into and out of these boxes into stock bottles. The same thing holds true of the various staining solutions that will follow.

Frozen Sections. Sections cut on the freezing microtome constitute a reliable and rapid method for quickly arriving at a diagnosis. They may be cut from fresh tissue and stained with polychrome methylene blue, but this usually takes time to learn and requires a good deal of skill, as it is difficult to handle unfixed tissue. Permanent and excellent sections are better prepared by the following method of Mallory and Wright.

Tissue is fixed by placing a block in 10 per cent formalin in a test tube and just

Sections are stained in hematoxylin, as usual. They are then transferred to the counterstain of ponceau, acid fuchsin, and orange G for five minutes. Next they are rinsed in acetified distilled water (see above). It is well to have a good supply of this on hand. Next they are mordanted in the phosphotungstic acid bath for a few minutes, rinsed in acetified water, and stained for five minutes in the light green dye, followed by a five minute immersion in acetified water to eliminate any excess of phosphotungstic acid. They are then dehydrated and mounted in balsam or Clarite.

The acetified water serves very much the same purpose as a "short stop" in photography, removing the excess of dye and keeping details precise. The phosphotungstic acid may be difficult to procure, and if so phosphomolybdic acid may be substituted and used as originally prescribed by Masson, although it does not give as good results, in my experience. This method is particularly applicable to cerebral tumors, in which case it often renders more complicated methods unnecessary.

SHORR'S SINGLE DIFFERENTIAL STAIN
This is somewhat similar to the preceding method in its color effects, although rather different dyes are utilized. It was originally devised for the purpose of staining vaginal smears to determine the degree of keratinization of the vaginal epithelium. While it was being used the discovery was made incidentally that it made an excellent and rapid method for staining tissue in general. It is composed of the following ingredients:

Biebrich scarlet (water-soluble)	0.3 Gm
Aniline blue	0.075 Gm
Orange G	0.125 Gm
Fast green (FCF)	0.025 Gm
Phosphotungstic acid	0.25 Gm
Phosphomolybdic acid	0.25 Gm
Glacial acetic acid	1.0 cc
Ethyl alcohol, 50%	100.0 cc

Again, it is easier to make up a larger amount so as to increase the individual

weights of the dyes and avoid the necessity of weighing them in milligrams. One should first stain the nuclei in the sections with hematoxylin, as already described, and follow this by a five minute immersion in the above "omnibus" solution, after which they are carried through 70 per cent, 95 per cent, and absolute alcohol and cleared in xylol to be mounted in balsam or Clarite, as usual.

GIEMSA'S STAIN When dealing with lymphoid tissue there is nothing as good as the Wolbach modification of Giemsa's stain, which requires fixation of the tissue in Zenker's solution. The dye may be procured in tablet form, put up by Burroughs and Wellcome, or the following stock solution may be made up:

Azure II eosin	3.0 Gm
Azure II	0.8 Gm
Methyl alcohol	
(Merck's reagent)	375.0 cc
Glycerol	125.0 cc
Combine and filter	

When tibules are used, they are dissolved in the methyl alcohol and the glycerol is added, the amounts of these are printed upon the containers. Of the stock solution one takes 2.5 cc, adds 3 cc of methyl alcohol, and dilutes the whole with 100 cc of distilled water to which 2 to 4 drops of 0.5 per cent sodium bicarbonate in aqueous solution have been added.

The mercuric chloride crystals are removed from the sections to be stained by immersion in Lugol's solution, followed by 5 per cent sodium thiosulfate. The sections are then rinsed and placed in the stain for an hour, after which the solution is changed for a fresh one and the sections allowed to stay in this overnight. They will be very deep blue and decidedly overstrained and must then be differentiated, each in turn, by immersion in 95 per cent ethyl alcohol with frequent examination under the microscope to determine how far differentiation has advanced. It is well to underdifferentiate, leaving them a bit darker than one wants them to be, as the subsequent baths

of alcohol and cleared in two changes of xylol.

It is advisable to carry out stains in glass boxes that hold ten slides each and to have a battery of glass-stoppered bottles. A dozen of these will be needed, as one requires two "descending" bottles of xylol, two of absolute alcohol, and two of 95 per cent alcohol, as well as two "ascending" bottles of 95 per cent alcohol, two of absolute alcohol and two of xylol. The bottles of the "descending" series are used for deparaffinizing the sections, those of the "ascending" series for dehydrating and clearing them after the stain has been completed. Cleared sections are blotted with finely grained "bibulous" paper and mounted under cover-slips in Canada balsam or Clarite, which is a plastic in solution in xylol that is largely replacing the yellower balsam.

MASSON-GOLDNER STAIN. Although hematoxylin-eosin is the standard stain in most laboratories, it has its disadvantages. Only the nuclei and a few substances like calcium and mucin take the hematoxylin, while everything else, including bone, cartilage, collagenous and elastic connective tissue, muscle, and nerve, stains red and must be recognized by its architectural characteristics. The Masson stain, as modified by Goldner and later by our laboratory, obviates these disadvantages by staining different tissues distinctively. To sum up very briefly one may say that the following general staining characteristics are found in this method:

Purplish Blue or Black (according to the hematoxylin used): nuclei; and calcareous matter;

Green: bone, cartilage, collagenous fibers, mucus, and the imperfect colloid of hyperplastic thyroids;

Port-wine Red: elastic fibers;

Golden Yellow: myelin sheaths of nerves;

Vermilion to Orange: keratinized epithelium, erythrocytes and fibrin;

Orange: mature colloid;

Pink: neuroglial fibers;

Red (or orange after Zenker fixation): muscle;

Rose Red: cellular cytoplasm;

Brilliant Vermilion: some zymogen granules, such as those of the intestinal Paneth cells.

One soon becomes accustomed to this galaxy of colors and is correspondingly well oriented as to the architecture of an organ when this stain is employed. It has been found to be far superior to hematoxylin and eosin as laboratory routine for this reason. The red colors are somewhat suppressed by formalin-alcohol fixation, but they are clear enough for every-day use. Zenker or Bouin-fixed blocks offer far more brilliant results, but it is well to cut down on the intensity of the orange G if Zenker-fixed tissue is being stained, as this tends to have an undue affinity for this dye.

The solutions are compounded as follows:

1. Harris hematoxylin is used as in the hematoxylin and eosin stain.
2. Counterstain:

Ponceau de xyloidine (Krall)	
or Xylidin ponceau	
(Hollborn)	0.2 Gm.
Acid fuchsin	0.1 Gm.
Orange G	0.1 Gm.
0.2% acetic acid in dis-	
tilled water	300.0 cc.

It is advisable to make up a stock solution ten times stronger than this and dilute it as needed, for weighing such small quantities of dye is otherwise laborious.

3. A 3 to 5% solution of phosphotungstic acid in water.
4. Light green (Lichtgrün, vert lumière) 0.1 Gm.

0.2% acetic acid in dis-	
tilled water	100.0 cc.

American dyes are now available and can be used in place of the German or French ones, but a little experimentation may be needed to adjust the concentrations to the desired point.

Sections are stained in hematoxylin, as usual. They are then transferred to the counterstain of ponceau, acid fuchsin, and orange G for five minutes. Next they are rinsed in acetified distilled water (see above). It is well to have a good supply of this on hand. Next they are mordanted in the phosphotungstic acid bath for a few minutes, rinsed in acetified water, and stained for five minutes in the light green dye, followed by a five minute immersion in acetified water to eliminate any excess of phosphotungstic acid. They are then dehydrated and mounted in balsam or Clarite.

The acetified water serves very much the same purpose as a "short stop" in photography, removing the excess of dye and keeping details precise. The phosphotungstic acid may be difficult to procure, and if so phosphomolybdic acid may be substituted and used as originally prescribed by Masson, although it does not give as good results, in my experience. This method is particularly applicable to cerebral tumors, in which case it often renders more complicated methods unnecessary.

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Glacial acetic acid	1.0 cc
Ethyl alcohol, 50%	100.0 cc

Again, it is easier to make up a larger amount so as to increase the individual

weights of the dyes and avoid the necessity of weighing them in milligrams. One should first stain the nuclei in the sections with hematoxylin, as already described, and follow this by a five minute immersion in the above "omnibus" solution, after which they are carried through 70 per cent, 95 per cent, and absolute alcohol and cleared in xylol to be mounted in balsam or Clarite, as usual.

GIEMSA'S STAIN When dealing with lymphoid tissue there is nothing as good as the Wobach modification of Giemsa's stain, which requires fixation of the tissue in Zenker's solution. The dye may be procured in tabule form, put up by Burroughs and Wellcome, or the following stock solution may be made up:

Azure II eosin	3.0 Gm
Azure II	0.8 Gm
Methyl alcohol	
(Merck's reagent)	375.0 cc
Glycerol	125.0 cc
Combine and filter	

When tabules are used, they are dissolved in the methyl alcohol and the glycerol is added, the amounts of these are printed upon the containers. Of the stock solution one takes 2.5 cc, adds 3 cc of methyl alcohol, and dilutes the whole with 100 cc of distilled water to which 2 to 4 drops of 0.5 per cent sodium bicarbonate in aqueous solution have been added.

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in alcohol will take out a little more of the stain. With practice, the microscopic control becomes no longer necessary. If the alcohol does not take the color out, this is because it has been "glass contained" instead of coming from a barrel, from which it absorbs rosin. In this case a few drops of 10 per cent alcoholic solution of colophonium will render the alcohol capable of differentiating the sections. These are then dehydrated by transferring immediately to absolute alcohol (omitting 95 per cent alcohol), cleared in xylol, and mounted in neutral balsam, Clarite, or oil of cedar wood. Ordinary balsam will cause rapid fading of the stain, as does exposure to sunlight. This stain gives the most satisfactory results for diagnosing lymphoid dyscrasias and brings out eosinophils in Hodgkin's disease in bold relief. It stains the lymphocytes fairly characteristically, but the azure elements are not as prominent as they are in blood smears fixed in saturated mercuric chloride in alcohol. Mitotic figures are also well demonstrated, and the stain may be used for a general survey of the bacterial flora of a given specimen.

PHOSPHOTUNGSTIC-ACID HEMATOXYLIN. This is a stain indispensable in the diagnosis of tumors of striated muscle, or for demonstrating loss of muscular striae in paralytic or inflammatory conditions of the striated muscle. It is best carried out on Zenker-fixed material, although other fixing fluids may give fair results. It is made up as follows:

Hematoxylin	0.5 Gm.
Phosphotungstic acid	10.0 Gm.
Distilled water	500.0 cc.

The hematoxylin and the acid should be dissolved in separate portions of the solvent, the hematoxylin with the aid of heat. When cool, they are combined and ripened artificially by the addition of 0.1 Gm. of potassium permanganate, which saves the time otherwise needed for spontaneous oxidation in sunlight, amounting to several weeks.

Sections are first mordanted by immersion in 0.25 per cent aqueous potassium permanganate for 5 to 10 minutes, followed by a wash in water and immersion in 5 per cent aqueous oxalic acid for 10 to 20 minutes. After a thorough rinsing, the sections are stained overnight or longer in the phosphotungstic acid hematoxylin, for which no differentiation is needed. If one desires nuclear details, mitotic figures in bold relief, and a good yellowish-red connective-tissue stain, five minutes in the permanganate and ten in the oxalic acid will be best; if one wishes deep blue striae in skeletal muscle, the timing should be reversed, the potassium permanganate being left on for ten minutes and the oxalic acid for five minutes. If the muscle is not then stained blue, a freshly prepared solution is indicated, for an exhausted and diluted solution will not produce brilliant stains in the case of muscle. This is also an excellent stain for demonstrating fibrin and neuroglial fibrils, both of which take on a deep ultramarine blue.

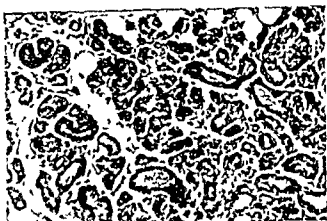
STAINS FOR INTRACELLULAR MATERIAL.
Mayer's Mucicarmine. This demonstrates mucin and is of value in the recognition of that substance in cells of doubtful lineage in some tumors. It will often clear up the diagnosis of small-celled carcinomas that otherwise might pass for sarcomas. It is made up as follows:

Carmine	1.0 Gm.
Anhydrous aluminic chloride	0.5 Gm.
Distilled water	2.0 cc.

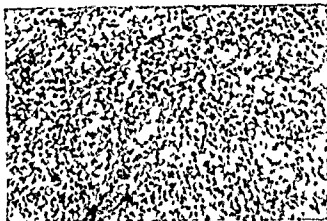
The ingredients should be combined and stirred over a low Bunsen flame or a hot-plate turned to "low," until the mixture becomes dark, whereupon the vessel is removed from the heat and 100 cc. of 50 per cent alcohol is added gradually, with constant stirring.

Best's Glycogen Stain. As the name indicates, this demonstrates glycogen and is useful in identifying that substance in "hy-pernephroid" tumors and chordomas. It is compounded thus:

PLATE I



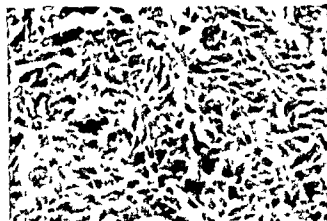
A



B



C



D



E

- A Masson trichrome light green stain of a plexiform hemangioma (to demonstrate general characteristics of the method)
- B Masson trichrome light green stain of a mucous carcinoma in situ from pyloric region. Note general bluish hue attributable to mucus accumulated in neoplastic cells
- C Section of chordoma of sphenoid region stained by Best's ammoniacal carmine method to demonstrate glycogen, which is bright red
- D Section of sclerosing hemangioma or "neuroxanthoma" stained by Perles' method, which demonstrates that contained pigment is hemosiderin by coloring this substance blue
- E Myelinated nerve from a splanchnicectomy. Note that Masson trichrome technic brings out reticular schwannian cytoplasm in orange or golden yellow

Carmine	2 Gm
Potassium carbonate	1 Gm
Potassium chloride	5 Gm
Distilled water	60 Gm

These should be combined and boiled cautiously for several minutes, then cooled, and 20 cc of 27 per cent ammonia in water should be added. The solution deteriorates rapidly and should be kept in the icebox in a tightly stoppered bottle.

In either method it is best to stain the nuclei with Harris hematoxylin for a minute or two, differentiate in warm water or hydrochloric acid, and then stain for from 5 to 20 minutes in the carmine solution. Mayer's method calls for no further treatment, in the Best method it is necessary to differentiate the sections in a solution composed of the following ingredients:

Absolute ethyl alcohol	80 cc
Methyl alcohol	40 cc
Distilled water	100 cc

The sections are treated with this solution for from one to three minutes, the fluid being changed until there are no red clouds. They are then rinsed in 80 per cent ethyl alcohol, dehydrated, and mounted as usual. In both these carmine methods the slides should not be put into water after the carmine stain has been completed, or it will be dissolved. Glycogen is very soluble in water, so that the only really successful fixation is in absolute alcohol. Celloidin sections are indicated for the best results, but it has been found that enough glycogen remains after paraffin embedding to afford very respectable sections.

PERL'S STAIN FOR IRON. In determining whether or not a given pigment is hemosiderin, which contains iron, it is often advisable to use a stain that will result in the Prussian blue reaction. For this purpose many good methods have been devised and will be found listed in such textbooks as Mallory's "Pathological Technique." A simple method is an adaptation of the original Perl technic in which sections are stained

with hematoxylin, differentiated in 1 per cent hydrochloric acid, and then rinsed so briefly in water that they remain reddish, as the iron reaction will be blue. The sections are then exposed to a mixture of 2 per cent potassium ferrocyanide and 1 per cent hydrochloric acid for one and one half to three hours. They are then rinsed in water and mounted in the usual manner after dehydration and clearing. A carmine nuclear stain such as lithium carmine or alum cochineal may be substituted for hematoxylin if still sharper contrast is desired.

STAINS FOR FATS AND LIPIDS. These must be carried out on frozen sections, as fats and lipids are soluble in the fluids used for embedding in paraffin. Two good methods are the Sudan III or IV and Nile blue sulfate (Lorrain Smith's). For the former, one of these dyes (orange and scarlet respectively) is dissolved in the amount of 1 Gm to 50 cc each of 70 per cent alcohol and acetone, C P. Frozen sections are cut, passed through 50 per cent alcohol into the Sudan solution, stained for ten minutes, and washed in 50 per cent alcohol. They are then transferred to water, in which they flatten out on the surface and dash hither and thither. It is because of this that the 50 per cent alcohol is employed so as to change the surface tension gradually, slow down their motion, and prevent their flying into shreds, as they would if introduced directly into water from the Sudan. They are then fished out, transferred to a Stender dish of Harris hematoxylin, and stained for one minute, after which they are differentiated in 1 per cent hydrochloric acid in another container and washed in water until they are well blued. After this they are mounted on slides and blotted almost dry, a drop of glycerol being placed on the section. Then a larger drop of glycerin jelly or glycerogel is dropped onto the section from a container that has been warmed in hot water. A cover slip is placed over this, and the jelly hardens as soon as it cools (which is almost immediately), and one has an almost permanent section. Nuclei are

blue, fat droplets orange or scarlet, according to the type of Sudan used.

NILE-BLUE SULFATE. This is much simpler and somewhat more satisfactory than the previous method. A deep blue solution of Nile-blue sulfate is made up in hot distilled water and filtered through filter paper. Sections from the freezing microtome are then stained in this for about ten minutes, after which they become deep, homogeneous blue. They are fished out on a bent needle or glass rod and differentiated in 1 per cent acetic acid until one can make out the architecture of the tissue in a general way, but this should not be carried too far, or one will have pale green and useless sections. After this they are rinsed in water and mounted in glycerol or glycerin jelly just like the Sudan sections, the alcohol being omitted because the staining solution is aqueous and the sections do not fly about on the surface of the water. Neutral fat will be stained rose pink, lipids (cholesterol ester, soaps, fatty acids, etc.) a rich navy blue, nuclei dark blue, and cytoplasm greenish blue. No counterstain is required. The stain is obviously more selective than Sudan III or IV.

Silver Impregnations. In these, silver is deposited on the structures that attract it as black, or as red colloidal metallic silver, a process that differs somewhat from staining. It has many analogies to photographic chemistry, depending upon developing (reduction of the silver), clearing surplus silver with hypo, and so on. The developing may even be carried out by exposure to sunlight. These impregnations are of great value in demonstrating the cytoplasmic processes of neuroglial or of ganglion cells, so that they are of great importance in connection with the diagnosis of tumors of nervous origin. Furthermore, the fact that silver impregnates reticulum and collagen gives it added importance in the diagnosis of reticulo-endothelial tumors. It may also be used in the case of tumors of the peripheral nerves to bring out fibrillary elements of the sheaths.

The basis for the most useful method is a solution of silver diamino carbonate made up as follows:

To 10 cc. of 10.2 per cent (equimolecular solution) silver nitrate in distilled water, strong ammonia is added drop by drop from a dropping bottle or pipet until the resulting precipitate is just dissolved. The process must not be carried too far or too hurriedly, and it is better to leave a few undissolved blackish grains of precipitate to insure that one does not overstep the end point. The mixture should be constantly agitated while the ammonia is being added. Ten cc. of 3.1 per cent aqueous sodium carbonate is then added. All the solutions must be made up of *distilled* water, particularly where the city supply is chlorinated, in order to avoid precipitates of silver chloride. Dilute this solution to 100 cc. with distilled water. It is best to prepare a fresh solution when it is needed, as it does not keep well in bulk.

IMPREGNATION OF RETICULUM. Paraffin sections are mordanted in 0.25 per cent permanganate of potash and 5 per cent oxalic acid as in the case of the phosphotungstic-acid hematoxylin technic: five minutes in the former and ten minutes in the latter. The sections are then washed in distilled water and brought into the silver diamino carbonate bath for one hour in an oven at 38° to 40° C. It is important to wash in several changes of distilled water after the silver bath. The sections are then reduced or "developed" in a solution of 1 cc. of concentrated formalin, 3 cc. of 1 per cent sodium carbonate buffer solution, and 96 cc. of distilled water, made up freshly before using. They are then washed in tap water and "toned" in 1:500 gold chloride solution, which replaces the silver with gold and may be used as long as it retains its golden yellow color. The sections are again washed well and intensified by immersion in a solution of 2 Gm. oxalic acid, 1 cc. of strong formalin, and water to make 100 cc.; this further reduces the gold salts and intensifies the impregnation. They are then washed and fixed in 5 per cent sodium thio-

sulfate ("hypo") solution in tap water for five minutes. After a final wash they are counterstained either with hematoxylin and van Gieson's stain or with hematoxylin and eosin.

Van Gieson's Stain

Concentrated aqueous solution
of picric acid 150 cc
Concentrated aqueous solution
of acid fuchsin 3 cc
Both of these should be saturated solutions

SILVER IMPREGNATION FOR NERVOUS TISSUE This is exactly the same as that for the impregnation of reticulum excepting that the mordant consists of equal parts of pyridine and glycerol in which the sections are immersed for 24 hours. This substitutes for the potassium permanganate and oxalic acid of the previously described method. The impregnation in the hot silver bath is advantageously prolonged from one hour to 2½ hours. No counterstain is necessary.

There is a very annoying tendency in these procedures for the sections to become detached from the glass slides during the shifts from one solution to another. The best way to prevent this is to dry the sections onto the slides in a warm oven or at room temperature for a week or more before attempting to impregnate them; it is also imperative that the slides be chemically clean and free from any grease.

MODIFIED RAMON Y CAJAL BLOCK IMPREGNATION This method is very valuable for demonstrating nerve endings and non-medullated nerves; it was devised by Nonidez. Here one must fix the tissue in 25 per cent chloral hydrate for 48 hours, after which the blocks are mopped dry with filter paper after being rinsed in distilled water. They are then transferred to 60 cc of 95 per cent alcohol to which four drops of ammonia have been added. In this they remain for 24 hours. After being rinsed a few minutes in distilled water they are placed in 15 per cent silver nitrate in the dark and in an

oven at 38° C for one week. They are then reduced in the following mixture:

Pyrogallol	2 Gm
Strong formalin	8 cc
Distilled water	100 cc

The blocks should stay in this overnight, at least 12 hours. They are then washed in distilled water for 3 to 4 hours and next immersed in 50 per cent alcohol for 6 to 8 hours. (The alcohol will turn yellow.) They are then dehydrated in 80 per cent alcohol overnight and run through acetone for one hour and chloroform for one hour. From this they are transferred to chloroform and paraffin (equal parts of melted paraffin and chloroform) in a paraffin oven, after which they are embedded in paraffin, two changes being used for 2 to 5 hours each. After being blocked in chilled paraffin in the usual way, sections are cut and may be deparaffinized and mounted in balsam or Clarite without counterstaining. If a counterstain is desired, they should be hydrated through descending percentages of alcohol in the usual way and stained with only the red and green elements of the Masson technic, omitting the nuclear stain. Without the counterstain the sections are yellow to brownish orange, with the nerve fibrils either dark brown (large neurones) or jet black (small neurofibrils and end organs). The counterstain colors the connective tissue jade green.

Elastic tissue Stains These are rather rarely used, indeed too rarely, but they are always profitable, particularly when one wishes to investigate pathologic changes in the blood vessels or in the subcutaneous tissue, where elastic fibers form definite patterns, the disarrangement of which may indicate pathologic degeneration.

WEIGERT'S STAIN This is composed of

Fuchsin, basic	2 Gm
Resorcinol	4 Gm
Distilled water	200 cc

The solution is brought to a boil in an enamel dish, and when it is seething briskly 25 cc of a 29 per cent aqueous solution of

blue, fat droplets orange or scarlet, according to the type of Sudan used.

NILE-BLUE SULFATE. This is much simpler and somewhat more satisfactory than the previous method. A deep blue solution of Nile-blue sulfate is made up in hot distilled water and filtered through filter paper. Sections from the freezing microtome are then stained in this for about ten minutes, after which they become deep, homogeneous blue. They are fished out on a bent needle or glass rod and differentiated in 1 per cent acetic acid until one can make out the architecture of the tissue in a general way, but this should not be carried too far, or one will have pale green and useless sections. After this they are rinsed in water and mounted in glycerol or glycerin jelly just like the Sudan sections, the alcohol being omitted because the staining solution is aqueous and the sections do not fly about on the surface of the water. Neutral fat will be stained rose pink, lipids (cholesterol ester, soaps, fatty acids, etc.) a rich navy blue, nuclei dark blue, and cytoplasm greenish blue. No counterstain is required. The stain is obviously more selective than Sudan III or IV.

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ous silver nitrate and are kept at 37° C in the dark for three to five days. The stronger concentration has been found better for tissue removed during life. The blocks are then washed in distilled water and developed in the following solution for from 24 to 72 hours at room temperature in the dark (shut into a dark closet or locker)

Pyrogallol	2 to 4 Gm
Formalin	5 cc
Distilled water	100 cc

After being washed in distilled water, dehydrated in 80 per cent, 95 per cent, and absolute alcohol, and cleared in oil of cedar wood, they are ready for embedding in paraffin through chloroform paraffin, xylol paraffin, or dioxane paraffin and two changes of pure paraffin in the usual manner. Thin sections should then be cut and deparaffinized, after which they are immediately mounted from the xylol in balsam or Clarite. The treponemata are black corkscrew like organisms on a yellow to yellowish brown background of rather indistinct tissue.

REFERENCES

GENERAL

The following textbooks have been drawn upon in connection with the writing of this book, and reference to them will be frequently made. They will not, however, appear in the lists of special references at the end of each chapter or section.

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ferric chloride is added. The mixture should be stirred and boiled for an additional two to five minutes. It is then cooled and the resulting precipitate is filtered off and the filtrate discarded. The filter paper with its charge of precipitate is then replaced in the evaporating dish, where some additional precipitate will be left adhering to the surface and 200 cc. of 95 per cent alcohol is poured in while heating cautiously. When the precipitate has dissolved, the solution should be cooled and made up to 200 cc. with 95 per cent alcohol. Finally, 4 cc. of hydrochloric acid (concentrated) should be added. This stock solution keeps well.

Sections are stained in the fuchsin solution for 20 to 60 minutes and then washed in 95 per cent alcohol. If they become overstained and diffuse they should be differentiated with 1 per cent hydrochloric acid in 95 per cent alcohol until the details of the tissue appear. They are then washed well in water. Next a nuclear stain is carried out, using hematoxylin and counterstaining with eosin, phloxine, or van Gieson's stain. The Masson trichrome stain is a superlative counterstain. There are other elastic stains, notably that of Verhoeff, for which the reader is referred to Mallory's textbook.

Staining Micro-organisms in Tissue. There are many staining methods for the demonstration of micro-organisms in sections of tissue, but few of them are used in connection with surgical pathology. The Giemsa stain is an excellent one to demonstrate the morphology of bacteria and protozoa, but it is not wise to attempt to identify the former by morphology alone, and it is much better to leave this to a competent bacteriologist. Tubercle bacilli are rather easy to demonstrate in pulmonary lesions and in those produced experimentally in lower animals, but when one attempts to find them in obvious examples of tuberculous lymphadenitis one is usually quite unsuccessful. Why this should be so is not clear, but it is a fact that one only very rarely succeeds in such instances. The kidney may also prove to be quite refractory in

this respect. One runs the best chance of locating tubercle bacilli if one searches in the pelvis of the organ or in the calices. As the surgical pathologist is often requested to carry out stains for tubercle bacilli and for *treponema pallidum*, two standard methods are given here.

STAIN FOR TUBERCLE BACILLI IN TISSUE. Sections fixed in the usual solutions are stained lightly with alum hematoxylin or Harris' formula and washed thoroughly until blue. They are then stained with carbol fuchsin, which is made up in the following manner.

Ziehl-Neelsen Formula:

Basic fuchsin in saturated alcoholic solution	10 cc.
Phenol water, 5%	90 cc.
(5 cc. melted phenol crystals shaken in 95 cc. water)	

Verhoeff's Formula:

Basic fuchsin	2 Gm.
Absolute alcohol	50 cc.
Melted phenol crystals	25 cc.

The sections should be stained in either of these formulas by steaming them on a hot plate for five minutes, leaving them in a paraffin oven for an hour, or allowing them to stand overnight in the solution at room temperature. They are then decolorized in acid alcohol (2 per cent HCl in alcohol) for 20 seconds. After they have been washed thoroughly in water to which 2 or 3 drops of ammonia have been added they are differentiated in 95 per cent alcohol, dehydrated in absolute alcohol, and cleared and mounted as usual.

LEVADITI METHOD FOR DEMONSTRATING TREPONEMA PALLIDUM. Blocks of tissue suitable for section are cut, not thicker than 1 mm., following 24 hours' fixation in 10 per cent formalin. The blocks are rinsed in water and soaked for 24 hours in 95 per cent alcohol, then they are put into distilled water until they sink to the bottom of the container, after which they are transferred to freshly prepared 1.5 to 3 per cent aque-

reach a given area in the body by entering through a hair follicle, by burrowing through membranes (endamebae, insects, worms), by introduction on contaminated instruments through wounds, or by hematogenous or lymphatic spread from one part of the body to another. Whatever be the cause, the reaction will be some type of inflammation which is a mechanism of defense that may or may not succeed in guarding the individual from further harm.

As has been indicated, there are three forms of inflammation which differ from one another in regard to the element of time (when considered by the clinician) and in respect to a different and characteristic histologic picture (when considered by the pathologist). Naturally, it is the histologic features that interest us here, and a description of the histopathology of each of the three forms must be presented before the subject can be made clear. One may briefly characterize all of them as consisting of exudates of elements of the blood or lymph in varying numbers and proportions of the cells that constitute the "formed" elements of the exudate. These are mainly hematogenous and include erythrocytes, neutrophils, eosinophils, and basophil polymorphonuclear leukocytes, monocytes, and their closely related derivatives of the reticulo endothelium, the macrophages. Besides these there are lymphocytes and lymphoblasts and thrombocytes or platelets. The cellular elements encountered in an area of inflammation may be assigned to two categories, the mobile and the fixed elements, of the latter, the fibroblasts and the vascular endothelium are the more important, the chondroblasts and osteoblasts responding only in certain types of injury to cartilage and to bone.

One may also distinguish between these cellular elements and the noncellular fluids which may be very important in bringing about repair, these are divisible into plasma (which contains fibrinogen), serum (which does not), and an indefinite fluid element known as "tissue fluid" which is found in

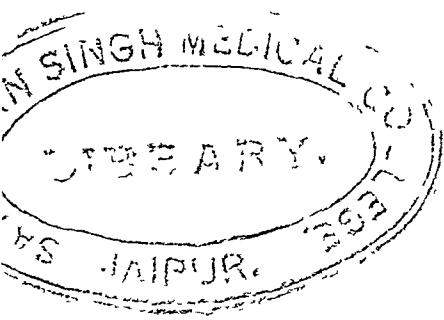
living tissue of any sort. These are the "humoral" elements.

Thirdly, there are various fibrillary elements such as collagen, which constitutes the white fibrous tissue, elastin, which is the substance of elastic or yellow connective tissue, and reticulin, which is of disputed composition and is found in the reticulum of the lymphoid tissue, the sarcolemma of muscle, the adventitia of vessels, and the loose areolar tissue that is more or less ubiquitous. Reticulin may or may not represent a distinct chemical entity. Although morphologically a fibrillary element, the fibrin which is precipitated from the fibrinogen of plasma and "tissue fluids" is not indigenous to normal tissue and is found only in conditions that indicate inflammatory reactions.

ACUTE INFLAMMATION

Acute inflammation is characterized clinically by a response to the various stimuli already enumerated, particularly bacterial infection, which takes on forms that vary in their intensity with that of the stimulus. As observed clinically, acute inflammation develops and subsides more or less rapidly, hence the term "acute", it may be mild, moderate, or violent according to the nature and degree of the stimulus. It is characterized by certain signs and symptoms that are classical: redness, heat, swelling, pain, tenderness, and loss of function of the affected part. The process may go on to local death of tissue, or necrosis, with or without the production of pus, it may subside and leave little trace of its presence, or it may spread and involve neighboring tissues or even those at a distance from the original lesion, should the infectious agent gain entrance to the blood stream or lymphatics.

The process, seen in sections under the microscope, may be accurately correlated with the macroscopic cardinal signs. In acute inflammation the morphologic elements are at first humoral or liquid, with a rapid accumulation of hemal cells—erythrocytes, polymorphonuclear leukocytes, mac



2

Inflammation

INFLAMMATION IN GENERAL

ACUTE INFLAMMATION

CORRELATION OF MICROSCOPIC WITH MACROSCOPIC SIGNS

EVALUATION OF INFLAMMATORY PROCESS

CHEMICAL FACTORS

PHAGOCYTOSIS

RESOLUTION

EVALUATION OF INFLAMMATORY PROCESS

(Continued)

REPAIR

SUBACUTE INFLAMMATION

CHRONIC INFLAMMATION

INFECTIOUS GRANULOMAS

GANGRENE

INFLAMMATION IN GENERAL

Detailed descriptions of the processes of inflammation and repair constitute early chapters in every textbook of general pathology, and if the reader has carried away any impressions of medical-school pathology he will certainly remember at least these first steps in the teaching of that subject. Nevertheless it seems advisable to recapitulate the rudiments of inflammation in this book, for the sake of completeness and as a review.

The surgical pathology of inflammation concerns itself chiefly with the morphologic characteristics of the three main classes of inflammatory processes: acute, subacute, and chronic. These are then used as standards for the diagnosis of inflammatory conditions in various tissues and organs and serve to establish certain facts that are of importance to the surgeon. It is imperative that the pathologist should recognize the fundamental differences between inflammation, repair, and neoplasia, differences which at times are very slight and are apt to lead to confusion in diagnosis.

Before proceeding to the consideration of the morphology of inflammatory processes, it might be well briefly to review the salient features that are common to a variety of forms of inflammation and to out-

line the successive stages in the progressive transition from the initial injury to the tissue, through inflammatory response, and thus to repair.

Inflammation may be said to be a response to some sort of injury, be it mechanical, thermal, chemical, electric, radiant, or (as in most instances) brought about by the invasion of the body by micro-organisms. Mechanical agents may act through contusion or crushing, incision or laceration; thermal injuries result from the raising or lowering of the temperature of the affected part above or below the limits of tolerance; chemical injury results from exposure to chemicals that act as poisons upon the tissues; electric injury is caused by the passage through the tissues of an electric current which may act electrochemically or may be accompanied by thermal injury as well; radiant injury is due to a variety of rays, usually from the extremes of the spectrum and including ultraviolet, infra-red, and x-rays. Infection, which brings about the majority of inflammatory responses, is the outcome of the introduction into the body of micro-organisms, either through their own action or by means of secondary agents such as sharp instruments or objects, insect vectors, and the like. Thus organisms may

compared with the cooler integument that surrounds the inflamed area and covers the unaffected tissue and undilated capillaries that do not overcome the normal cooling effects of the atmosphere. To put it another way, the more blood that circulates beneath the skin the warmer will that area of skin feel to the touch, the less blood there is, the cooler will it feel.

Pain and Loss of Function These are symptoms and cannot be observed in microscopic sections, although one may readily infer their presence in the clinical examination. Pressure upon sensory organs and dilatation of the neural sheaths account for the pain, the loss of function depends upon this and upon the swelling which produces unwieldy members and clumsiness. Tissue may be destroyed and evoke mechanical reasons for loss of function, as when tendons and ligaments slough away.

EVALUATION OF INFLAMMATORY PROCESS

Mere correlation of gross clinical features with the microscopic appearance of inflamed tissue is not enough to cover the entire process, we must try to explain the successive stages of the reaction as best we may from their inception to the stage of healing and restitution of the area to normal. This is difficult, because the elements in the inflammatory process may respond in varying proportions under varying conditions. Sometimes, as in the case of a mild burn or the action of light (sunburn) or of a chemical irritant, the humoral elements predominate and there is little exudation of a cellular type. Again, there may be much hemorrhage or it may be trifling. The amount of fibrin precipitated will vary noticeably with the case, but one is never sure as to the reason for this. An infection with the hemolytic streptococci will usually be characterized by intense hyperemia and hemorrhage (cf. the lungs in influenzal pneumonia complicated by streptococcal infection), the pneumococci are noted for provoking a heavy precipitation of fibrin, the staphylococci may cause intensely puru-

lent exudates. For these reasons it is well nigh impossible to describe the stages of acute inflammation in a step by step fashion, the best one can do is to present a picture of those that are observed in the development and healing of an abscess, such as a boil.

We have described the exudation of fluid elements and some of the possible reasons for their presence. The deposition of fibrin is supposed to afford a framework upon which leukocytes, which are good crawlers but poor swimmers, can move about in the waterlogged tissue, it may also serve to entangle bacteria and thus immobilize them. Plugs of fibrin may assist in walling off the inflamed area and preventing the escape of the inflammatory agents. This is all obviously argument on a teleologic basis, that the fibrin may have other purposes may be determined in the course of investigations such as those of Menkin, although at present these are the theories he has offered to explain the question. He has recently summed up his findings in a paper, "Chemical Basis of Inflammation" which is based on data obtained in the course of many experiments and has the merit of attempting to explain the phenomena of inflammation on a basis other than one of pure reasoning or teleologic interpretation which, in the past, tended to endow the leukocytes with a sort of individual, purposive intelligence that would be most improper in ameboid cells.

Chemical Factors Menkin has isolated a number of substances in the globulin fraction of extracts of inflamed tissue: a euglobulin "necrosin," a pseudoglobulin the "leukocytosis promoting factor," and an unidentified nitrogenous material "leukotaxine." Whether these are or are not chemical entities is uncertain, but Menkin's experiments have demonstrated that injection of necrosin will produce many of the phenomena of acute inflammation, notably necrosis, in laboratory animals. In experiments capillaries became blocked in the area of the injection, and if the substance

rophages and monocytes, and later lymphocytes and plasma cells with a scattering of eosinophil leukocytes, all of which may appear in the tissue spaces very soon after the fluid elements have produced edema. As the inflammation increases fibrin will be precipitated from the plasma and the cells of the affected area will show evidence of damage, at first degenerating and then undergoing necrosis. In the latter case they either become dissolved (cytolysis) or broken up into granular particles of *débris* (cytorhexis). The cells may, on the other hand, become more compact and refractile without either dissolving or breaking up: this is known as "coagulation necrosis" in contradistinction to the other type, which is called "colliquation necrosis."

CORRELATION OF MICROSCOPIC WITH MACROSCOPIC SIGNS

Redness. In this the capillaries are engorged and are dilated to several times their normal caliber: there appears to be an abnormally large number of these on account of the fact that many of them represent practically closed and collapsed channels under normal conditions, opening up only in response to a need for hyperemia or increased blood in the affected area. Dilatation results in an increased quantity and decreased rapidity of the flow of blood, and neutrophil leukocytes begin to accumulate along the endothelium of the vessels and to penetrate their walls, emerging into the surrounding spaces in the perivascular tissue. An added factor in the slowing of the circulation apparently consists in a locally increased viscosity of the blood which aids in retarding the rapidity of its flow. The reason for leukocytes' adhering to the endothelium is said to be two-fold: the lining of the vessels becomes viscous or "sticky" and a variety of theoretical substances in the tissues about the vessels exert an attraction for the leukocytes, causing them to penetrate the walls.

Swelling. Naturally the expansion of all the vessels with an increased amount of

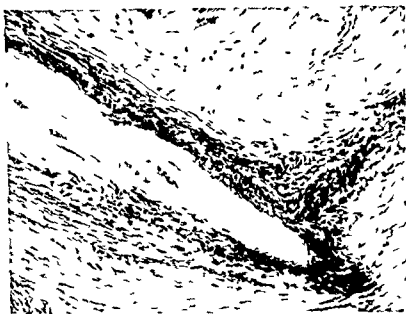
blood in the affected area will increase its bulk and appear as swelling, but in addition to this there is an outpouring of the humoral elements (plasma and serum) which soon produces an edematous or "waterlogged" state of affairs and is thus the prime factor in causing swelling. One cannot see this fluid under the microscope; one merely sees the effects of its presence in the form of separation of tissue elements and the formation of irregular, unstained spaces between them. Only when fibrin is precipitated or when the albuminous contents of the fluid is coagulated by the fixative can one observe morphologic evidence of its presence. These fluids serve several purposes: they dilute the irritants, they furnish antibodies to combat organisms by agglutinating them or by neutralizing their toxins, and they constitute a sort of natural irrigation that washes decomposed material out of the inflamed areas. In the last case they may, unfortunately, afford a means for spreading an infectious agent or irritant as well as for combating it.

During the period of fluid exudation the leukocytes leave the vessels in increasing numbers and, along with them, erythrocytes and platelets are carried through the capillary walls. The leukocytes penetrate these in an active manner, like small amebae; this is exudation. The erythrocytes and platelets do it in a passive way; this is diapedesis. (The terms are old and poorly adapted, for the word "exude" implies an oozing out, while "diapedesis" means "going through on foot.") Added to these phenomena is the possibility of an actual breach in the wall of the vessel, through necrosis, in which case the cells of the blood leave the vessel as hemorrhages. Thus the presence of immigrating hemal cells adds to the bulk of the inflamed tissue and the swelling.

Heat. The production of local heat is a matter of relativity: there is no actual increase in local temperature aside from that associated with the generalized febrile reaction which may be present. The local dilatation of capillaries causes a focus of apparent warmth in the overlying skin as

Resolution Having followed the progressive stages of local inflammation thus far we come to a turning point toward resolution, in which the microscope reveals new participants in the defensive struggle. Although the stage of resolution is beginning, however, that of inflammation continues in certain areas for some time before it completely subsides. The new elements are the lymphocytes. Concerning these, Rich, whose

advanced concerning the functions of these cells. If the contention that they are transformed into macrophages (advanced by Maximow and Bloom) is correct at least a part of their functions would be evident, but this assumption has as yet but little confirmation by other observers. That they might be instrumental in producing antibodies has long been surmised, but never conclusively proved.



Tip of wooden splinter embedded in sheet of fascia. Reaction to this foreign body is local and largely composed of macrophages which are not forming foreign body giant cells.

excellent article on inflammation has been most helpful, says

I am sure that all who are engaged in the study and teaching of pathology will agree that the complete ignorance of the function of this cell is one of the most humiliating and disgraceful gaps in all medical knowledge.

Congregated often in the most peripheral parts of the lesion, they have the appearance of phlegmatic spectators passively watching the turbulent activities of the phagocytes. Literally, nothing of importance is known regarding the potentialities of these cells other than that they move and that they reproduce themselves."

There is no need to clutter this description with the speculations that have been

The macrophages, which appear shortly before or at the same time as the lymphocytes, are much better understood. That they have a scavenging function is obvious, but their origin has been the subject of acrid disputation, unlike the leukocytes and small lymphocytes they are capable of multiplying rapidly by mitotic division. They are ubiquitous, being found in the blood as monocytes or blood histiocytes and in the tissues as macrophages or tissue histiocytes. They have many aliases, such as "chiasmocytes," "dust cells," "heart failure cells," "Touton cells," "xanthoma cells," "lepra cells" and so on, as the case may be.

It seems probable that they are self sustaining in the circulating blood, where it is

was injected intravenously, secondary lesions were caused elsewhere. The leukocytosis-promoting factor causes a lively leukocytosis through stimulation of the bone marrow when similarly injected. The third substance, leukotaxine, provokes local emigration of leukocytes from the capillaries and, unlike the leukocytosis-promoting factor, causes leukopenia in the circulating blood.

As acute inflammation progresses, the polymorphonuclear leukocytes that have played the most important part in the histologic picture (at least as regards numbers) begin to break up and to disappear. Many of them may have become a prey to the infectious organisms, but too many disappear too suddenly to make this explanation at all complete. After removing bacteria and destroying fibrin at the site of inflammation they appear not only to have served their purpose, but to have favored their own destruction. The hydrogen-ion concentration of the tissue in an inflamed area is at first low, but becomes progressively acid as time passes. Menkin has determined that leukocytes flourish in an alkaline medium but begin to disintegrate in a neutral one and go to pieces altogether in one that is definitely acid. It is also known that monocytes and macrophages can exist in an acid medium, and it is a fact that these cells succeed the polymorphonuclear leukocytes in the area of inflammation, multiply in situ (which they cannot do, being incapable of cell division), and very soon outnumber them, taking their place and removing the cellular debris left by the interaction of the inflammatory and defensive agents.

Bacteria are dealt with in a number of ways: they are actively phagocytosed by leukocytes, they are agglutinated by defensive antibodies (agglutinins) so that they cannot spread and multiply readily, and their toxins (when produced) are diluted by the serum, which may contain antibodies that neutralize such substances (antitoxins). The hydrogen-ion concentration influences bacteria as well as polymorphonuclear leu-

kocytes, and as acidification of the inflamed area progresses, a point is reached where the medium is too acid to permit bacterial existence. Some bacteria cannot thrive in a temperature much above the normal degree for a given host, so that fever, in elevating the temperature, may be considered a defense mechanism in some instances. Unfortunately there are other bacteria that grow better at temperatures well above normal, so that this point is of questionable significance. Anaerobic organisms may be combated by hyperemia, which furnishes more oxygen to the infected area; this mechanism is well illustrated in the case of gas gangrene, in which the bacteria grow well in the necrotic and ischemic portions of the lesion, but die off and cannot thrive in those where blood is still actively circulating.

Phagocytosis. This has been mentioned, but not yet discussed. It is known that phagocytes are attracted to organisms when both are suspended in warm hanging-drop cultures. When bacteria have been engulfed by the cells they are either digested by proteolytic ferments (Opie, Longcope and Donhauser, etc.) or, as Rous has shown, the intracellular pH may fall to 3 or less, an acidity at which the usual pathogens cannot exist. There is a question as to whether the attraction exerted by micro-organisms upon leukocytes (chemotaxis or chemotropism) has not been overemphasized; leukocytes are constantly on the move and experiments in the hanging drop seem to indicate that they will eventually collide with the bacteria in the course of their peregrinations. Once this occurs, however, the organism is promptly engulfed. That leukocytic locomotion is hastened or slowed by changes in temperature and pH is known, that they travel no faster toward bacteria than they do when directed elsewhere in the drop was shown by McCutcheon and Dixon, although it was noted that when they reached the immediate vicinity of the organisms they were then "strongly attracted."

After such fibrils have been precipitated they are apparently "arranged" into a net work by the movement of the slowly creeping macrophages or the branching spikes of proliferating fibroblasts or young capillaries "fibroglia fibrils," much stressed by F B Mallory and his pupils, are intracellular fibrils that lie within the cytoplasm of the fibroblasts and are demonstrable chiefly, if not exclusively, in Zenker fixed blocks

The fibrils of early granulation tissue are at first very delicate and sinuous and impregnate black with silver, as time passes they become associated into bundles that are made up of coarser fibers and impregnate red Mallory and Parker claimed that this was a matter of the smaller fibers becoming more readily impregnated than those of coarser dimensions, so that the silver became more readily reduced The same idea was revived by Nageotte and Guyon, who went into a lengthy discussion of the subject from the physiochemical point of view and decided that reticulin and collagen were identical To the writer, however, the ideas that seem more nearly correct are those of Siegfried and of Mall that reticulin differs chemically from collagen in possessing a phosphorus atom which may be attached in a side chain If a chemical substance extracted from reticular tissue and presumably reticulin be left standing in water for a few days at room temperature it will take on the staining characteristics of collagen, which might indicate that it had become hydrolyzed to that substance Furthermore, it is easy to find tiny fibrils that impregnate red with silver and almost as easy to discover some that are partly red and partly black Size, then, seems to play a very negligible part in the staining reaction

The fibrillary network just discussed becomes denser as the area heals and collagen begins to predominate The fibers become thicker and ultimately lie in dense bundles that, by their contraction, compress the capillaries and gradually produce relatively avascular cicatricial or scar tissue Acutely

inflamed organs, such as the gallbladder and appendix, undergo a similar process as the acute inflammation subsides, but in such cases the term "fibrosis" is used instead of "cicatricial tissue"

If acute inflammation is widespread without forming a definitely circumscribed area like an abscess, one speaks of "cellulitis" or "phlegmon" In the case of circumscribed groups of numerous small abscesses in the



Topographic photomicrograph of a caruncle The innumerable black dots are polymorphonuclear leukocytes

hair follicles of the skin the term "caruncle" is usually employed If the process is limited to one definite and well circumscribed area the condition is known as an "abscess" The common boil is a subcutaneous abscess arising in a single infected hair follicle

Foci of acute inflammation may become extensively pigmented if there has been much hemorrhage, the hemoglobin that is released from the erythrocytes as they break down becomes elaborated into hemosiderin when it is taken up by the phagocytes This has a yellowish brown color, presenting as small amorphous masses and granules in the cytoplasm of the phagocytes

SUBACUTE INFLAMMATION

This is a common phenomenon in the appendix and gallbladder, and it may repre

demonstrable that they multiply in veins tied off by ligation; they exist in the areolar tissue as histiocytes or wandering cells and may be seen to multiply when the occasion calls for an increase in their numbers. They may also recapitulate their embryonal history and be produced by the detachment of reticulo-endothelial cells in the sinuses of lymphoid organs, but this is possibly only an emergency measure. They share the phagocytic proclivities of the polymorphonuclear leukocytes, but can take up far larger bits of particulate matter (hence "macrophages") than can these. They are not limited in their diet; one may find erythrocytes, lymphocytes, polymorphonuclears, or fragments of any of these within them, or granules of pigment or lipids. If foreign material is too large for one of them to englobe, they fuse to form the familiar "foreign-body giant cell" and surround (if they do not succeed in destroying) the offending particle, which may be suture material, feces, foreign material like dirt or splinters, and the like. Thus they "neutralize" such substances by surrounding them with a coating of living protoplasm.

Repair. When the stage of inflammation has reached a point where the *débris* has been largely removed from the affected area, resolution is nearing completion and repair is initiated, but there is again overlapping of the two stages and they are not clearly separable. The so-called "fixed cells" of the tissue, or fibroblasts, begin to multiply in the sound tissue at the periphery of the lesion, and they either grow into it by forming branching cords of proliferating cells or wander into the more central regions and establish islands of rapidly growing cells. Before the advent of the tissue culture it was not known that they were sluggishly ameboid and motile, hence the name "fixed cells"; they are not fixed at all. At this stage of the process the fibroblasts and macrophages may resemble one another morphologically, but moving pictures of tissue cultures will reveal marked differences in their behavior. The macrophage is

more actively motile and it constantly emits cloudy pseudopodia that take up fluid ("inocytosis"). When it dies it appears to explode in a leisurely fashion, represented as an upheaval of sorts when the motion picture is speeded up to 90 times the usual speed. The fibroblast, on the other hand, is sluggish, shows no active pseudopodia, and when it dies it simply becomes opaque and inert without manifesting any of the dramatic explosive phenomena just mentioned.

Together with the sprouting and immigration of fibroblasts, there is a similar growth of no less energetic angioblasts that carry new capillaries into the devastated area—capillaries that may become so exuberant as to form projecting reddish loops or granules on the surface of the new tissue and give it the name of "granulation tissue."

With the multiplication of the "fixed" cells there is a production of intercellular fibers. These can be readily demonstrated as having nothing to do with the fibrin that precedes them by the simple expedient of staining such tissue according to a reliable method for dyeing fibrin and impregnating simultaneously with silver. The latter will color collagen red and reticulin black, leaving the fibrin unaffected and free to take its specific dyes (phosphotungstic-acid hematoxylin or the Gram aniline-blue stain). There are no transitions between fibrin and these newly formed fibrils. That these are produced by macrophages and fibroblasts seems to be only indirectly true, as the cells appear to cause precipitation of small granules in the fluids of the tissue and these then fuse to form chains of beads and ultimately fibrils. Maximow has demonstrated this in tissue cultures of macrophages, and Roulet and Doljanski have shown that the fibrils may be formed in plasma separated from a culture of macrophages by a porous porcelain plate that would permit the passage of hypothetical precipitants from the culture, but would have pores too narrow to permit the passage of the macrophages themselves.

refers to the specific lesion of tuberculosis. The majority of tubercular lesions are tuberculous, because this disease is far more prevalent than are others that produce similar granulomatous foci, but it should be understood that there are many of them that have nothing to do with the tubercle bacillus. Such lesions are, in reality, a response to a foreign material that is not readily disposed of: lipids, fatty substances, waxes, *paraffin*, some plant spores like *Lycopodium* powder, and the like. Long ago Hensen discovered that dead tubercle bacilli when injected into experimental animals could produce typical tubercles, and this observation was confirmed and expanded by other investigators, who found that the injection of particles of grain, such as farina, would do the same thing. Therefore it is not strange that we should find nonspecific tubercles studding fistulous tracts about the anus, where fecal material acts as the foreign body. Similarly, destruction of adipose tissue will release liquid fat that can provoke a tubercular reaction, as in Darier's sarcoid and in panniculitis. Unabsorbed bits of suture, spores introduced on rubber gloves with *Lycopodium* powder, and even bits of dirt or other foreign material that may be ground into the skin during trauma may all produce tubercular reactions with resulting "foreign body tubercles."

Tuberculous Granuloma. The specific tubercle is the unit lesion of tuberculosis, wherever it may develop, in its classic form it consists of a giant cell or two and a mass of epithelioid cells which are swollen macrophages, surrounded by a peripheral zone of lymphocytes and plasma cells all bound together by reticulum produced by the epithelioid cells. Such tubercles usually arise in the proximity of small vessels, occasionally one may demonstrate the fact that they represent a form of organized thrombus at the site of bacterial accumulations within such vessels. The lesions tend to fuse with neighboring ones, forming conglomerate tubercles, and to undergo a form of cheesy central necrosis known as "caseation" and

usually diagnostic of tuberculosis. The participation in the lesion of giant cells (known as "Langhans giant cells"), which are merely foreign body giant cells, has been explained by Sabin and her co-workers as attributable to the presence of waxy materials that may be chemically isolated from extracts of tubercle bacilli and presumably emanate from the "acid fast" portion of the organisms. Other material may be isolated as well and found to attract macrophages, when injected experimentally, without producing any giant cells, so that the reaction may be explained on a chemical basis.

Boeck's Sarcoid or Lupoid. In the disease generally known as "sarcoidosis of Boeck" the unit lesion is similar to that of tuberculosis, but it is considered to be a separate entity by many authorities. In it one notes epithelioid cells and giant cells, together with a tendency toward reticular fibrosis. Caseation does not occur, and the giant cells may contain peculiar inclusions like starfish, or perhaps vaguely crystalline, which are known as "asteroid bodies." They do not always appear in the lesions, but their presence is helpful as a diagnostic sign. They have been described in connection with other foreign body giant cells. The lack of caseation, the more marked formation of reticulum in the tubercles, and the inclusion bodies are all of value in making a differential diagnosis.

Luetic Granuloma or Gumma. In the tertiary lesions of syphilis the unit lesion is often very similar to the specific tubercle, it differs from it in classical cases in so far as it is chiefly composed of lymphocytes with fewer macrophages. The primary lesions of syphilis, on the other hand, are more like ordinary chronic inflammation, rather vague and uncharacteristic and differing from this chiefly in the presence of vascular lesions, such as angitis and endothelial proliferation. Instead of undergoing caseation, the tertiary gumma tends to necrose at its center in such a way as to leave blurred vestiges of the histology of the tissue. This is a sort of coagulation necrosis

sent either a continuing acute inflammation at a somewhat reduced tempo or an inflammation that begins and continues in a mild acute form. The so-called "strawberry gallbladder" of surgical parlance is a good example of the latter process. The gross appearance of subacutely inflamed tissue resembles that of acute inflammation, but it is subdued and less striking. Under the microscope one observes the same cellular elements as those enumerated in connection with acute inflammation, but there are less polymorphonuclear neutrophils and more lymphocytes, plasma cells, and eosinophil polymorphonuclears. The presence of the last is common to subsiding acute and subacute inflammation, but we have no very good explanation for this empirical observation. As such cells characterize allergic reactions, one might suppose that they appear in the above instances in response to a sensitization of the tissues by the absorption of split proteins due to decomposition in the inflamed area. They are very commonly noted in the neighborhood of degenerated or necrotic cancers, particularly those of the uterine cervix, which might strengthen the validity of this hypothesis.

Subacute inflammation, then, is a condition that occupies a position between acute and chronic inflammation, and it is none too well set off from either of these.

CHRONIC INFLAMMATION

There are two general types of chronic inflammation: the ordinary, diffuse, and nonspecific variety and the specific type noted in the infectious granulomas. From the standpoint of pathology, the term "chronic" is applied somewhat differently from the manner in which it is employed by clinicians; chronic inflammation may supervene in an acute phase, but it usually begins as a chronic process that has a definite morphology. It somewhat resembles the late stages of acute inflammation, inasmuch as its most important constituent is the lymphocyte, less importantly the macrophage and eosinophil. It is accompanied by

fibrosis in many instances, which lends it a further resemblance to repair, but it differs from this because it may be destructive.

It is not known why the lymphocytes appear in such numbers in chronic inflammation; their immature, proliferative form, the lymphoblast, may occasionally be noted in this process, but it is usually absent. Therefore one must suppose that lymphocytes migrate into chronically inflamed tissue from lymphoblastic centers such as the lymph nodes, splenic follicles, and the like. Lymphocytes infiltrate an area of chronic inflammation diffusely, they may be a little more numerous at its margins, but there is little active breakdown of the resident cells of the involved tissue, and hyperemia is usually moderate. As the process progresses, plasma cells, which are supposed to originate from lymphocytes, become more and more evident. Apparently the lymphocytes acquire more cytoplasm and their nuclei acquire radiating clumps of karyoplasm which gives them the appearance of cart wheels. Mature plasma cells are polygonal and more or less pyriform, the nucleus occupying the narrower pole of the cell. Very occasionally one observes very large plasma cells that are probably produced by similar changes in lymphoblasts; hence they are known as "lymphoblastic plasma cells." In some forms of chronic inflammation of lymphoid tissue plasma cells develop small fuchsinophil granules that grow within the cytoplasm of the cells and fuse to form large globoid bodies that ultimately escape into the tissue spaces and may be mistaken for mycotic organism, such as yeasts or blastomyces. These fuchsinophil bodies are known as "Russell bodies"; their significance is yet to be explained.

INFECTIOUS GRANULOMAS

A more specific type of chronic inflammation is less diffusely distributed in the tissue and tends to form tubercular lesions. In this connection let us stress the difference between "tubercular" and "tuberculous"; the former means "like a small bulb," the latter

Lymph nodes Observed grossly, they have the appearance of abscesses rather than that of caseous tubercles, under the microscope they are found to consist of necrotic centers filled with pus and cellular debris (which may simulate protozoan organisms) that are surrounded by palisades of epithelioid macrophages and occasional giant cells. They thus combine the microscopic picture of an abscess with that of a tuberculous lesion that has been secondarily infected. If one suspects that a given lesion is of this variety, the specific antigenic Frei test should be carried out on the patient to confirm the diagnosis.

Xanthogranuloma A poorly recognized lesion, because it is rarely observed, this is sometimes noted in lymph nodes, particularly those of the axilla and groin, or it may occur subcutaneously. It is sometimes erroneously diagnosed as tuberculosis. The cutaneous lesions resemble indolent boils raised, red, and angry looking, although comparatively painless. Under the microscope well formed tubercles are found, with epithelioid and giant cells and a suggestion of central caseation, in addition, one notes large numbers of foam cells (Touton or xanthoma cells) that are macrophages heavily laden with droplets of lipids. Outside of the tubercles the tissue may contain many plasma cells, and these may actively produce Russell bodies.

Plasma cell Granuloma Small granulomatous lesions composed almost entirely of plasma cells may be found at the apices of dental roots (apical abscesses), or in any focus of chronic inflammation, being particularly common in the urinary bladder in some forms of chronic cystitis and in the rectum. Some of them may represent the rectal lesion of lymphogranuloma venereum, which is radically different from that noted in the lymph nodes in this disease. Such plasma cell granulomas must be carefully distinguished from plasmacytic myelomas.

Hodgkin's Granuloma The most granulomatous lesions of Hodgkin's disease of the lymphoid organs may be included here,

although they will be described in that section dealing with these diseases.

Diffuse Composite Chronic Reactions There are a number of mycotic diseases in which the lesion is essentially chronic, but which may show areas of acute or subacute inflammation as well. In blastomycosis, or

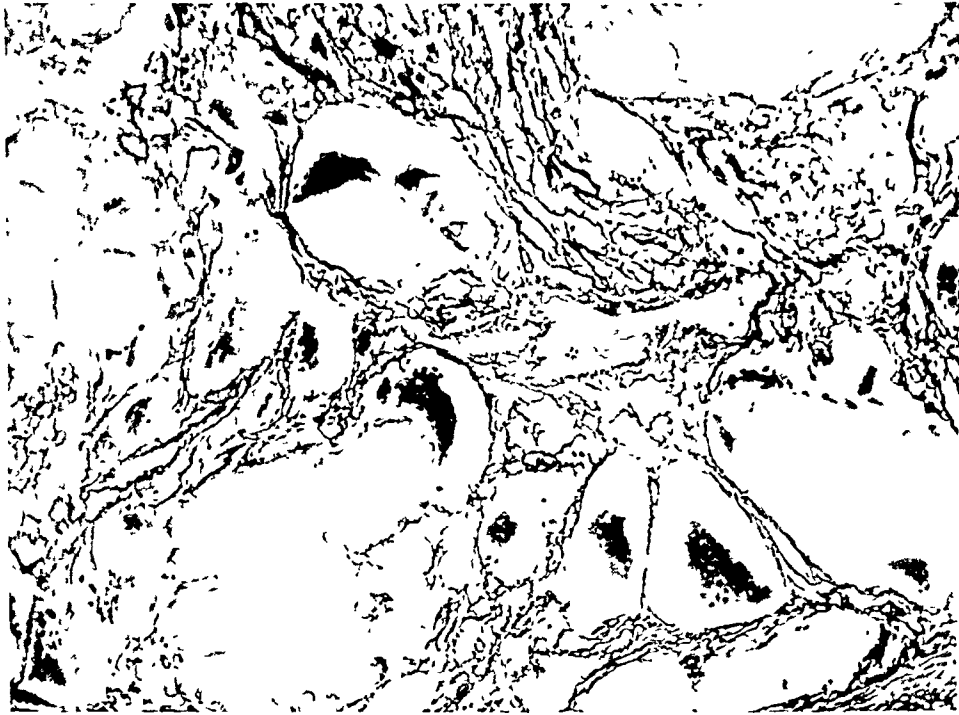


Organism of coccidioidal granuloma in focus of inflammation in suprarenal. This illustrates nuclear multiplication of *Coccidioides immitis* (Col F H Foucar)

coccidioidal granuloma, there are areas of diffuse chronic reaction, often surrounding fistulae, with a wealth of plasma cells, lymphocytes, and foci of macrophages and giant cells that are rather too poorly delimited to qualify as tubercles. In the cytoplasm of the giant cells one eventually finds spherical bodies with refractile doubly contoured outlines that are blastomyces, coccidioidal granuloma, prevalent in the states of the Far West, shows a similar lesion, but the organisms are more complicated, contain material that stains well, and thus differ

that imparts a rubbery consistence to the lesion, as noted macroscopically, which led to its being called "gumma." It is quite characteristic of the gumma that it should lie within the lumen of an artery, and one may often demonstrate this by staining sections for elastin, when the internal elastic lamina of the vessel will be seen to lie near

material, surrounded by a palisade of epithelioid cells among which, however, there are relatively few if any giant cells. They undergo marked fibrosis and may eventually become almost completely converted into fibrocalcareous masses. They may, however, be mistaken for tuberculous lesions if one is unacquainted with the source of the ma-



Silver impregnation demonstrating formation of reticulum in a gouty tophus filled with urates and foreign-body giant cells. (Compare with illustration of reticulum in giant-celled tumor of bone in Chapter 6.)

the periphery of the miliary gumma. It is also noteworthy that the neighboring vessels will show angiitis, often of a fairly acute and pronounced type. In diagnosing luetic lesions it is always well to know whether or not the patient has shown a positive Wassermann reaction.

Rheumatoid Nodules. These are usually observed in the vicinity of joints (juxta-articular nodes or tubercles) and may present on the dorsum of the fingers in a different form which is then known as "Heberden's nodes" (see *Fascia, Tendons, and Ligaments* in Chapter 5). They are much less cellular than are the granulomas just described and consist of caseous centers in which there is usually abundant calcareous

material and does not take pains to examine the lesion carefully.

Tophi. Foreign-body reactions to urates deposited in the subcutaneous tissue are known as "gouty tophi." These may ulcerate through the skin and discharge their crystalline contents upon the surface, or they may erode the underlying bone. They are composed of epithelioid and giant cells and, as microscopic sections are usually washed in water, the urates are dissolved and only the acicular spaces that contained them may be observed under the microscope.

Lymphogranuloma Venereum. The lesions of this comparatively recently recognized disease may simulate those of tuberculosis when they occur in the inguinal

a peculiar resonance is elicited. The tissue undergoes rapid and spreading necrosis which is due both to the closing off of the blood supply and to the direct action of the bacteria that swarm in the infected tissue. One may note small bubbles or spaces in the tissue which shows the signs of acute inflammation and gangrene, and may also observe the large encapsulated bacilli which are readily stained with the ordinary dyes. There are other members of the genus of *Clostridium* that cause similar lesions, but infection by these is not as common as that by *Clostridium welchii*.

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from the blastomyces, which are yellowish, have such dense capsules that they may be quite unstained, and resemble the ova of worms. Actinomycosis may produce similar lesions, but there will be foci of acute inflammation that amount to abscesses and in these foci colonies of the ray fungi, or actinomyces, may be stained, particularly if Gram's method is employed.

Leprosy. In the tubercular form of leprosy which produces nodular cutaneous lesions that are extremely disfiguring, the microscope will demonstrate a rather diffuse packing of the subcutaneous tissue, extending down from the pars papillaris of the skin by innumerable foam cells within many of which one may demonstrate lepra bacilli, often clumped into the characteristic "cigar bundles." The lesion will be described in detail in the section on dermal lesions; suffice it to say here that it is essentially a granulomatous one in which macrophages play the stellar rôle, their degenerated forms being known as "lepra cells."

GANGRENE

There seems to be little reason for gangrene to be described with any degree of meticulousness; it is the result of interference with the circulation to a part and represents mass necrosis of that part. Generally speaking there are two types: dry and moist. The former is a process of mummification in vivo. Arterial obstruction through thrombosis, arteriosclerosis, or destruction of important arterial trunks through trauma of whatever sort prevents the blood from circulating in the affected part, so that it shrivels up and becomes discolored and dry like the limb of a mummy. It acquires a peculiar odor rather closely resembling that of poorly cared-for feet. Moist gangrene, on the other hand, may be due to partial obstruction of the circulation, or the presence of specific bacteria (*Aerogenes capsulatus*, *Clostridium welchii*, etc.), or to venous obstruction; blood can come to the part, but cannot get out of it. The result is an inflamed, moist, weeping, and foul-smelling

member that is much more malodorous than it would be were the gangrene of the dry variety. Here, the odor resembles that of garbage.

Microscopic examination of such material shows that which might be expected: there is cellulitis in the case of moist gangrene, necrosis in that of the dry. There is nothing particularly characteristic to be noted, and one may arrive at the diagnosis by gross examination. The greenish black discoloration is usually the result of the decomposition of extravasated blood from damaged vessels, much like that which occurs in the case of contusions with local hemorrhage.

When gangrene occurs in internal organs it may be the result of mechanical obstruction of vessels through torsion, of compression by adhesions or membranous bands, or of pressure exerted by narrow ring-like openings such as the necks of hernial sacs; it may be the outcome of thrombosis or embolism of terminal arteries, following infection or as a result of emboli from the heart. It is always moist gangrene, as the affected part is bathed in serous exudate from the peritoneum. An entire loop of bowel, an appendix, or a gallbladder will then become blackened or discolored. The odor exuding from the affected part is fishy and foul. Microscopically speaking, one may determine this condition by the presence of mass necrosis, loss of all nuclear detail in the native cells, and extensive hemorrhage and deposition of fibrin in the tissue spaces.

A specific gangrene, caused by the Welch bacillus, is the well-known "gas gangrene" in which death of tissue is due to a massive and overwhelming infection by a capsulated bacillus that is most frequently found in manured soil and is introduced into penetrating wounds together with bits of such soil. The bacillus is a gas-producing anaerobe, so that there is added to the cardinal signs of inflammation another sign that is pathognomonic of gas gangrene: crepitus. The affected tissue crackles when palpated, as though it had been inflated with air, and when the finger is run rapidly over the skin

a peculiar resonance is elicited. The tissue undergoes rapid and spreading necrosis which is due both to the closing off of the blood supply and to the direct action of the bacteria that swarm in the infected tissue. One may note small bubbles or spaces in the tissue which shows the signs of acute inflammation and gangrene, and may also observe the large encapsulated bacilli which are readily stained with the ordinary dyes. There are other members of the genus of *Clostridium* that cause similar lesions, but infection by these is not as common as that by *Clostridium welchii*.

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Healing of Surgical Wounds

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HISTORICAL PERSPECTIVE

In the early days of the century "surgical pathology" was a term restricted to the study of wound healing, in Keen's System of Surgery, for example, the section on surgical pathology dealt not with the subjects taken up in this book, but with various types of healing in a variety of tissues. Books on surgical pathology did not consider, as we are now doing, the pathologic conditions that are encountered at and treated by surgical operations, rather they were limited to discussions of the gross and microscopic phenomena of the healing of wounds in all their varied aspects. Courses on this subject kept students drawing diagrammatic representations of healing wounds. For several weeks armies of leukocytes, fibroblasts, and other cells were made to march and countermarch across the pages of drawing books. Microscopic sections of healing wounds in rabbits' ears were prepared on the second, fifth, seventh, fourteenth, and thirtieth day after they had been experimentally produced, and the students spent dreary hours in endeavoring to draw graphic representations of these. The process was then repeated on infected wounds, healing fractures, and the like, with lectures to point

the application of the facts that had thus been learned. It would therefore be quite unsuitable not to consider this subject at some length in the pages that follow in this chapter.

OPERATIVE INCISIONS

Before performing an operation the surgeon chooses that incision that will best serve the purpose of obtaining adequate exposure and, at the same time, insure the best opportunity for firm and solid union of the severed tissues after the operation is completed. In the case of the appendix, for example, it is perfectly possible to make an incision straight through the wall, beginning with the skin and continuing down to the peritoneal cavity, but will this insure a firmly knitted wound after the operation? Will it prevent the possibility of a subsequent herniation of the intestines through a scar that is weak and thus allows the peritoneum to bulge outward through the line of the incision? These questions will be answered inferentially below.

Another type of incision might be the "right rectus" variety, which enters the sheath of that muscle, the belly of which is then pulled aside, the abdomen is entered through the posterior layers of that sheath

When the muscle falls back into place as the incisions are subsequently closed, it will interpose a strong layer of muscular tissue in the line of closure and thus reinforce it.

Suppose, now, that the McBurney "grid-iron" incision be employed. In this case the skin will be incised over "McBurney's point," which lies at the junction of the outer third with the inner two-thirds of a line drawn from the anterior superior spine of the ilium to the umbilicus. The incision will run across this point from above downward and roughly parallel with the inguinal ligament. When the sheath of the external oblique muscle is encountered this will be severed, and the fibers of the muscle will not be cut, but will be separated at a sharp angle to the line of the incision. Next, those of the internal oblique muscle will be treated in the same manner, but as they course roughly at right angles to those of the outer muscle, they will be separated in that direction. Finally the transversalis fascia and peritoneum will be opened and the operation carried out through this opening, in which the incision runs in one direction, the lines of separation of the underlying muscles in two more, and that of the underlying fascia and peritoneum in still another. When the time for closure arrives and the incision is sutured the uncut fibers of the muscular layers will scarcely require any stitching together as they will naturally fall into place, the outer crossing the inner at an angle.

It naturally follows that this last method will insure the firmest, strongest, and most reliable closure and insure the patient's getting up and about much sooner than would the other two, in which more healing would be necessary. It is not always possible to employ such ideal incisions, but where they are possible the surgeon usually prefers to use them.

HEMOSTASIS

While a surgeon is operating it is necessary that all bleeding should be controlled, and permanently so. The surgeon who backs

out of an operative field leaving any oozing vessels behind him runs the risk of impeding the healing process, of producing hematomas that must later be evacuated or left to organize and heal themselves, and of leaving a moist and traumatized site which is more easily infected. Therefore vessels are caught in hemostatic clamps as soon as they bleed and are tied off with catgut or silk if they are sufficiently large to require tying. Small vessels often cease bleeding once they have been well pinched in the clamp. This is the result of the contraction of the muscular coat of the vessel plus the plugging of its narrowed extremity by a blood clot, the production of which is favored by injury to the endothelium and the release of "tissue fibrinogen" from the wall of the vessel.

When a vessel is cut and tied that is the end of it as a continuous duct, but it is not the end of its circulation which seeks collateral vessels, by-passes the interruption, and re-enters the lumen of the severed artery through lateral branches below that interruption. Thus the tying of the vessel has created no permanent defect in the circulation. In the case of terminal arteries that do not possess collateral anastomoses, however, one must cut and tie as little as possible.

ASEPTIC OPERATIVE CLOSURE

When the surgeon has completed an operative procedure he "sews up." Sutured and closed under aseptic conditions the series of operative wounds he has created should heal by primary intention.

Sutures. The divided edges of any severed tissues are brought together by strands of material that is either absorbable or unabsorbable; the use of the latter is limited by some surgeons to those parts of the operative site where it may be readily removed, such as the skin. By passing deep sutures through the skin and tying them on its surface they, too, may be withdrawn when their usefulness is over. In withdrawing such sutures the surgeon cuts between the knot

and the skin at one side of the wound as closely as possible to the surface, and then pulls them out by the knot. This prevents drawing any considerable length of suture that has been contaminated back through the tissue. Failure to observe this procedure may initiate infection of the tract of the suture, which would be one kind of stitch abscess.

SUTURING MATERIALS Some operators employ silk for almost everything, including tying off vessels. While silk is commonly considered unabsorbable, within the course of six weeks or so it is often completely destroyed in the tissues by being phagocytosed. It is always surrounded by phagocytes which fuse to form foreign body giant cells, and the fibers of silk may be found in a fragmented and variously digested condition within the cytoplasm of these syncytia, or near groups of them.

There are other unabsorbable materials. Horsehair was formerly sterilized and used for cutaneous suture, silkworm gut (which is familiar as leaders and snells to the angler) may be utilized for "stay" sutures, and various sorts of wire may be utilized for these, or for "through and through" sutures that are employed in rapid emergency work. The stay suture is a strong, deeply set, temporary stitch that is placed so as to reinforce the actual line of closure of an incision. It is valuable when there is tension to be overcome, either in fat subjects or when much skin has been sacrificed and the edges are difficult to approximate.

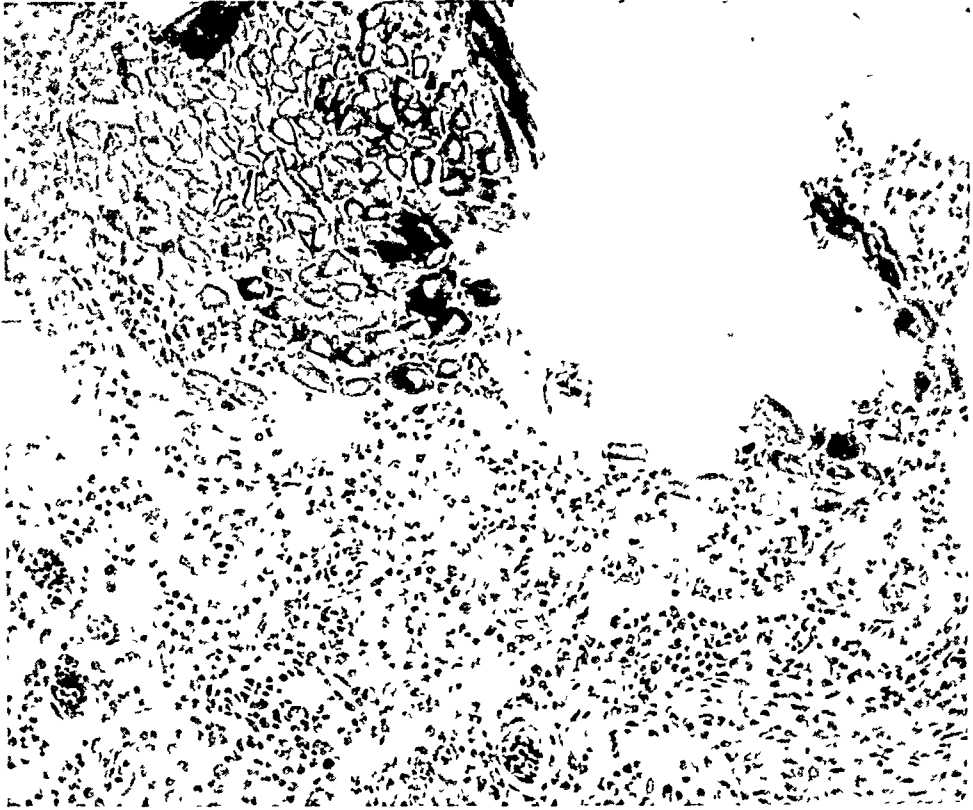
Of the absorbable materials catgut is a good example, placed in deep situations in the operative site it is soon removed by phagocytosis after it has begun to soften and break up (within a week or so) after having served its purpose of holding the tissue together until healing takes over that function. By chromicizing catgut, slowly absorbable material is created which will resist absorption for several weeks. This is used, of course, when the reinforcement of sutures is desirable for a longer time than would be afforded by ordinary catgut. It

may be deeply placed with the assurance that it will disappear in a month or less. Silk is often used in its stead.

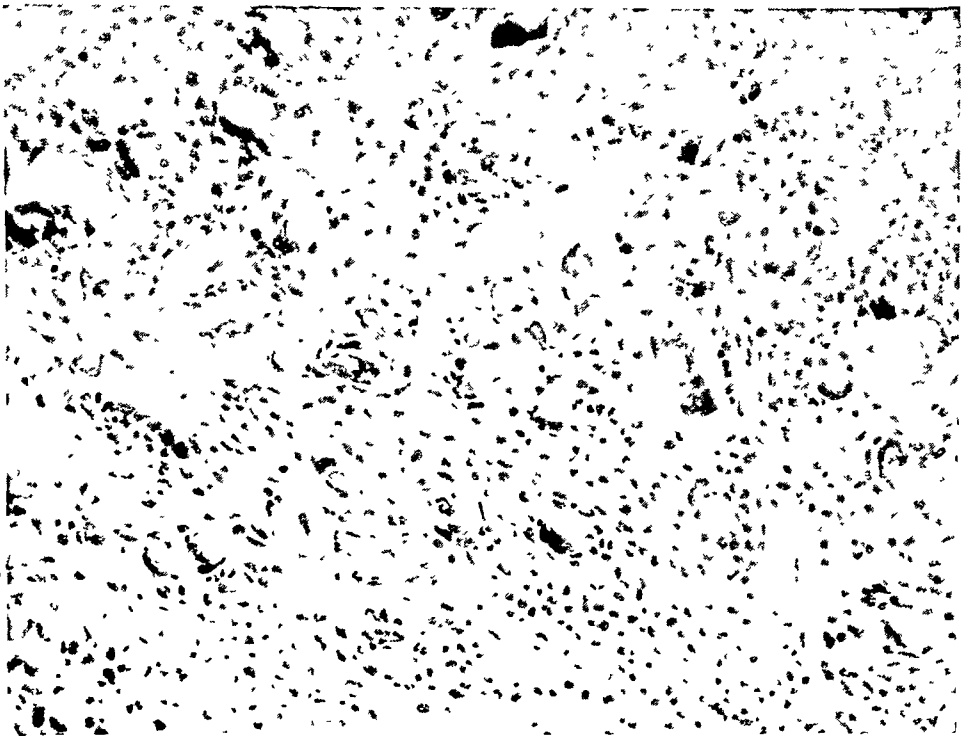
Suture material, then, is used to tie off vessels as they are cut and to approximate severed muscles, visceral walls, mucosal surfaces and the like. It then unites the edges of the operative incision from its inner to its outermost layer. It may also be utilized to reinforce the immediate line of closure in the form of stay sutures placed at intervals along and outside of this.

SUTURING METHODS The surgeon usually prefers to unite each layer of severed tissue to like tissue as he closes his operative wound, this is called "closing in layers." It is manifestly best that fibrous tissue should be united with fibrous tissue, muscle of one layer with that of the same and not of another layer, fascia with fascia, fat with fat, and skin with skin. In that way each layer will be restored as closely as possible to its original integrity and maintain its original function. Beginning at the peritoneum, this is closed and each muscular layer sutured within the limits of that layer. The fascia is closed, if there is a thick adipose layer a few stitches may be used to approximate this, and the skin is finally sewn up as smoothly as possible.

The neat approximation of the cutaneous wound is not merely a matter of cosmetic effect, bunches and gaps in the line of suture will produce fibrous scarring which may delay union and may cause pain over considerable periods. The gaps will have to be closed by the formation of granulation tissue, and this, in turn, will have to be organized. One could bunch all of the tissues together in the bight of a through and through suture or two and "get away with it," as fibrous connective tissue would take care of the union, but there would be a thicker scar and there would be less chance of regeneration of the various layers across the line of closure. Sometimes this method must be resorted to when there is great urgency and speed is necessary to save life.



Silk suture (shown as group of black triangles) and reaction about it after a few weeks' stay in wall of colon. Note that there are very few giant cells.



All that remains of silk suture after six months of phagocytic action by giant cells. Note vacuoles in cytoplasm of these; they indicate dissolved material from sutures.

PRIMARY WOUND HEALING

As soon as the severed tissues are approximated and almost before the patient is back in bed, the process of healing commences. This process is exactly similar to that which has been described in the chapter on inflammation. There is a minimal exudate of fibrin and leukocytes between the tightly apposed surfaces of the wound so that fibroblasts begin bridging the insignificant gap and capillary sprouts are soon pushing their angioblasts from one lip of the wound across to the other. This begins to knit the wound together with a network that is at first little more than a gossamer network of no value in holding the tissues together but which, for the present, acts as a scaffolding upon which firmer fibrous tissue will be laid down. Shortly after this, reticular and collagenous fibers are produced and begin to lend to the wound some tensile strength.

During the first stage of healing, up to the fourth or fifth day, it is relatively easy to separate the lips of a wound apart with the thumbs, after the fifth day it becomes increasingly difficult or impossible to do this, so firmly is the tissue amalgamated by the fibers in the young scar. At about this time the function of the sutures begins to be superseded by these fibers, and one may remove those that are accessible. One soon learns from the appearance of a wound when it is feasible to withdraw the sutures. This varies with the individual and with the state of that individual's health.

A subject who is poorly nourished and lacks the necessary vitamins will frequently exhibit exasperatingly slow healing of an operative wound. This is often observed in victims of gastric lesions in whom absorption and digestion are impaired. It is noteworthy that elderly people, who might reasonably be expected to heal their wounds slowly, often show remarkably rapid healing of superficial incisions.

After the initial stage of healing of the wound is past, there is progressive fibrosis

attributable to the formation of collagenous tissue. This may go on to the production of keloids in some instances, overshooting the mark and producing thick, ropy scars. Normally the process should reach a maximal degree and then not only stop, but undergo recession. In many instances this subsidence is so complete that it may be difficult to



Section through simple aseptic incision after one week of healing. All that can be noted is linear disarrangement of architecture of corium running through middle of picture perpendicular to surface of skin. There is slight deformity of the epidermis.

locate the site of a past operation, its scar having become almost invisible. This is true also in the case of the deeper wounds of the operation, such as those in intestinal mucosa. The redness of the overlying tissue persists for several months, giving way to complete pallor in the case of most successfully performed operations. The redness is due to hyperemia in the increased vascular network in the newly formed scar, as the collagen increases it exerts pressure on these vessels and closes them partially or completely.

Thus, to sum up, the process of healing passes through three stages: conglutination with minimal acute inflammation, organization with hyperemia, and fibrosis with ischemia.

REGENERATION OF TISSUE

In carrying out any extensive operation the surgeon severs a number of varieties of tissue; it might be interesting to note whether these are capable of regenerating across the lines of cleavage he has created, or whether they are merely united by a fibrous band or scar, as one might join two pieces of silk by sewing them to a strip of cotton tape.

Fibrous Tissue. Naturally, where fibrous tissue has been divided its regeneration is complete. This is also true of vascular tissue within the limits already discussed in connection with the tying-off of vessels.

Nervous Tissue. When a nerve has been severed, even if the ends are sewn together again, all the axons it contains will degenerate back to their parent cells, possibly in the spinal cord or a ganglion. Those distal to the line of severance will also die, as they are cut off from the parent cell. There will be regeneration, however, and shortly fibers are pushing down the nerve trunk to the breach in the nerve, regenerating from their respective cells. It may take some time for this to happen, and there may be some delay in getting through the fibrous barrier that will have formed between the severed ends of the nerve. Once past this they will continue down the distal segment of the nerve to its distribution. Nerves often exhibit great tenacity in breaking their way through fibrous scars; sometimes they are unable to do so and may form small tumor-like growths which will be described in the chapter on the pathology of the nervous system. Naturally, anesthetic areas develop in the distribution of severed nerves and persist until regeneration is complete. If regeneration does not take place the anesthesia becomes permanent.

Muscular Tissue. Smooth muscle, which is often severed in intestinal, uterine, and other operations, appears to have little power of regeneration. The line of closure of the defect in such muscle is very narrow, so that the interposition of a thin layer of

fibrous scar at this point makes little difference. Should it become hyperplastic, however, and then contract there might be stricture of the lumen of the affected viscus.

Skeletal muscle often exhibits regenerative phenomena that are readily observable; the nuclei of the sarcolemma multiply so as to form a sheath of closely set structures about the severed end of the myofibril. These appear to be carried out with the regenerating portion of the fiber so that they are ultimately properly spaced. Occasionally very immature myoblasts that look like foam cells will appear apparently from nowhere in particular and proceed to multiply so as to replace lost muscular tissue. They seem to have been lurking about as a sort of reserve, but one seldom finds them in normal muscle, so that their appearance in connection with regeneration is more or less mysterious. It is noteworthy that this regeneration is more often seen in connection with myositis than it is with reparative processes after mechanical injury.

Cardiac muscle, being a combination of smooth and striated muscular tissue, exhibits only slight capacity for regeneration. A strong fibrous scar in the heart appears to be able to take the place of severed muscle, as it does in the case of the intestines, and to bridge effectively the gap in wounds that are occasionally effectively sutured. It is well known that scars which follow infarction after coronary thrombosis may cause very little dysfunction.

Cartilage and Osseous Tissue. Cartilage is repaired in much the same manner as is bone, which we shall presently consider in a more detailed fashion. It regenerates from chondroblasts of the perichondrium and may also be produced by osteoblasts of the periosteum and endosteum. As it is normally a part of osteogenesis under some conditions this is not strange. It is of importance in connection with injuries to joints and osteochondral junctions such as those of the costochondral connections of the sternum

As we shall not discuss fractures elsewhere, the fundamental points in their healing will be taken up here. There are several types of fracture. In young subjects whose bones are still fairly fibrous and "soft," the fracture may take the form of a long split in the shaft with a small line of actual fracture at one point. This may penetrate the shaft for a few millimeters only. Such a fracture is known as a "green stick" fracture, a term that is self-explanatory. In older subjects, whose bones are more brittle and more extensively calcified, the bone is snapped in two, sometimes fairly cleanly, at others with a good deal of splintering and fragmentation. Occasionally a bone may merely be split or cracked, without any displacement of the fragments. As there is no deformity, no false point of motion, and only pain to indicate the severity of the trauma, the x-ray is called upon to demonstrate such splitting fractures.

If the fragments do not penetrate the soft parts after a fracture has occurred, one speaks of a "simple fracture", should they penetrate to the surface, piercing the soft parts and causing lacerated wounds, it is known as a "compound fracture." It may be produced by violent trauma which crushes and lacerates the overlying parts, exposing and fracturing the bone, or it may result from the violent displacement of the sharp fractured ends of bone which are forced through the soft parts to the outer air. With compound fractures, therefore, there is always the possibility of the introduction of infectious matter into the wound with consequent infection and inflammation of both soft parts and bone.

After such fractures have taken place it is the function of the physician to approximate or "set" the ends of the fragments to facilitate healing or "knitting" and to unite the broken bone, restoring its integrity. It is not necessary that the fragments should be in good approximation, for the formation of a callus (to be described later) may unite even overriding ends of a fractured shaft, but such a union will be bulky, there will be

shortening of the shaft and the process will require much longer than it would were the ends accurately apposed. This is accomplished by means of one's tactile sense, or with the aid of actual observation with the fluoroscope. It is next necessary to insure immobility, so that healing may proceed uninterrupted by the tearing and irritation that would be occasioned by motion at the point of fracture. This is accomplished through the aid of splints or by means of steady traction, weights are attached to the extremity and, through their pull, prevent overriding of the fragments.

The first result of a fracture is the outpouring of blood from injured vessels and the marrow of the bone. Thus blood clots, as there is plenty of fibrinogen set free from the injured tissues to insure this. Organization of the clot then takes place, and a fibrous scar is formed in exactly the same manner as has been described in the case of injury to soft tissues. The process may stop here, particularly if the patient is old and infirm, producing a simple fibrous union that, while it holds the fragments together, lacks any of the requisite rigidity of bone and creates a permanent false point of motion in the shaft of the injured bone. This occasionally occurs in connection with young people who are unable to mobilize sufficient calcium to insure ossification of the fibrous union. Such failures are attributable to dietary deficiency, dyscrasias of the parathyroid glands, and similar causes.

When ossification sets in it follows the process usually observed in the formation of bone in the normal embryo. The periosteum is the chief source of osteoblasts in the long bones, the endosteum sharing to a lesser degree. For this reason surgeons seek to preserve the integrity of stripped periosteum when performing operations on bones, so that this may produce new osseous tissue to fill any operative defects. In the fracture, osteoblasts proliferate and emigrate from the periosteum into the fibrous scar, arranging themselves in the lines that will be taken by the trabeculae of the future

bone. Others perform the same function at the inner side of the shaft around the marrow cavity. Thus a ring of osteogenic tissue is created about the ends of the fracture (periosteal or ring callus), between the fragments themselves (intermediary callus) and on the inner side of the shaft extending upward and downward into the medullary canals for a short distance (internal callus). At first this tissue is largely composed of osteoid tissue, which lacks calcium and appears like a network of hyaline trabeculae of connective tissue that has the general architecture of true bone. With time this becomes calcified and the osteoblasts become enclosed in it within lacunae or lined up along the trabeculae. The periosteal callus tends to overgrow and to form a superabundant, fusiform collar about the fracture, but this gradually becomes more and more compact and ultimately almost disappears through the slowly destructive action of osteoclasts that are essentially phagocytic foreign-body giant cells.

As the bone forms, marrow is regenerated and grows into the newly formed callus, its osteoclasts hollowing out a new system of haversian canals and being instrumental in restoring the bone to its normal architecture and reducing the total amount of callus. In this way a fracture in which the apposition of the fragments has been accurately accomplished will heal so perfectly that one has difficulty in demonstrating it a few years later. Usually there are slight nodular excrescences at the site of the fracture.

Should a fracture be of the comminuted variety, in which shattering injury has broken the bone into many small fragments, these may be completely isolated from any vascular supply and will, if large, undergo necrosis. If they are tiny they will be destroyed and removed by the phagocytes and osteoclasts. During ossification there is an increase in the phosphatase of the blood, and an adequate supply of calcium and phosphates must be at hand to insure rapid and smooth completion of the process. In order that these substances may be absorbed

from the diet there should also be an ample amount of vitamins A, C, and D present. If the fracture is comminuted it is often necessary to open the soft parts over it and to "débride" the wound; this means to remove the débris by instrumental means, taking out all large and isolated fragments and repairing any extensive lacerations in the soft parts about the ends of the fractured bone. Sometimes it becomes necessary to wire these together, or to join them by means of bone plates that are screwed into place. Such a débridement will often hasten matters appreciably by removing in a few minutes masses of fragmented bone that would require weeks for absorption or extrusion by natural means.

Adipose Tissue. This is a matter of relatively little importance, as fat is seldom destroyed in large quantities and its regeneration in wounds of various types is not necessary for the well-being of the tissue in general. In fact very adipose subjects often pose problems in operative procedures on account of the thick sheets of oily, soft, and unmanageable fat that they possess. There is a possibility of regeneration from embryonal lipoblasts that apparently lie dormant in adipose tissue and are somewhat analogous to the myoblasts in skeletal muscle in that respect. These lipoblasts are the "mulberry cells" of embryology; they multiply and produce mature fatty tissue under some circumstances. Fat is an extraordinarily labile tissue, undergoing hypertrophy and atrophy with the greatest facility, but its regenerative powers are not very marked in spite of this.

SECONDARY WOUND HEALING

Should an operation be carried out upon an already infected area, or should an operative wound become secondarily infected through some accident or slip in technic, the process of healing is necessarily modified and more complex. Let us take, as an example, an appendicectomy which is already complicated by the presence of an appendiceal abscess. Formerly any operative area

of this sort was subjected to a rigorous flushing with hot saline solution that turned the operative field into a veritable morass of bloody fluid. Then a drain was laid in the wound so as to afford exit for any purulent matter or serum that might be exuded from the walls of the abscess and accumulate there. Nowadays there is comparatively little of this excessive "toilet of the wound", the sucker that is connected with a mechanical suction apparatus is employed to remove the excess of exudate, the wound is lightly sponged out, and the rest is left to nature. It is remarkable how well the peritoneum will take care of any subsequent exudate and the meager remnants of that which has largely been removed by suction. Drains, too, are used sparingly and placed only at strategic points. The advent of the sulfonamide drugs makes it possible to dust a wound lightly with these and to cut down the growth of infectious organisms to a minimum. They are by no means inevitably used in operations of this sort.

Drains. A word about drains is in order. At first it was believed that a metal or rubber tube would act as a conduit for purulent or serous discharges, but such tubes were easily clogged by clots or by dried discharge. They were superseded by the "cigarette drain," which is a wisp of gauze wrapped in rubber dam. The original idea was that the capillarity of the gauze would conduct the discharge to the surface and that the rubber dam would prevent adhesion of the drain to the granulation tissue. These drains are still used, but now their purpose is conceived to be that of keeping the wound open, and affording drainage along their surface while the gauze inside acts merely as a soft cushion. Capillarity was found to function only just so long as the discharge did not clot or dry in the meshes of the drain, and this clogging was found to be a matter of a few hours. Drains are also made by rolling up rubber dam into an elongated, only more or less tubular structure that will act in the same manner as the cigarette drain.

The chief function of drains is to act as safety valves by keeping open a tract from the depths of the wound to the surface. Along this tract any accumulation of fluid may escape on the surface, should it not there is always danger of the abscess re-forming, with the whole procedure to be repeated.

Healing by Granulation. An infected wound, therefore, will either fail entirely to close or will close only partially, instead of the apposed edges being amalgamated by organization, they will gape apart and a layer of soft granulation tissue will form over their surfaces. Eventually, after the infection has subsided, this tissue will become organized and gradually close in the defect by steadily encroaching upon it. Then there will be a broad mass of cicatricial tissue interposed between the edges of the wound. As this slowly heals in this manner a tract may persist, running from its depths to the outer surface of the body. Such a tract is known as a "sinus," or a "sinus tract." If it should communicate with a hollow organ such as the intestine or urinary bladder it will be called a "fistula" (meaning a "little whistle"). Such a tract may become superficially epithelized if dermal tissue grows downward into it, this materially interferes with its closure by healing, as epithelium interposes an insurmountable barrier between the granulating surfaces. Epithelization of such tracts is much overemphasized in the literature, practical examination of hundreds of them proves that they are usually lined not with epithelium, but with granulation tissue. Should such a tract communicate with the intestines a fecal fistula, discharging feces, would result, should it communicate with the urinary bladder a urinary fistula would be formed. In a like manner one observes salivary, pancreatic, biliary, and other varieties of persisting fistulae.

When wounds covered with granulation tissue can be successfully cleaned up and rendered reasonably aseptic by means of irrigation with Dakin's solution or the use

of sulfonamide drugs, it is sometimes possible to draw the surfaces of granulation tissue together by means of aseptic adhesive tape, or properly placed sutures. This hastens the process of healing by permitting organization to spread from one granulating surface to the other, and it is sometimes spoken of as "healing by third intention."

EPITHELIZATION

A wound is never completely healed until it is firmly covered over by a layer of regenerated skin. In a clean wound the epithelium bridges the insignificant gap at the outer end of the operative tract in a very short space of time by growing across it from either side. Epidermal cells spread out in thin sheets that meet and fuse at the center of the incision and then proceed to differentiate into epidermis which is complete from basal to keratinized layer. The dermal adnexa, however, such as hairs, sebaceous glands, and sudoriferous glands do not regenerate.

In infected or gaping wounds, where there is a good deal of granulation tissue and a considerable space between the edges of severed skin, the growth of sheets of epithelium becomes more marked and encroaches upon the area of naked granulation tissue so that one may observe that this is being gradually covered by thin, reddened skin with a rather dry, yellowish, and sunken margin at its outer rim. Little by little the uncovered area of granulation tissue becomes narrowed down until it is completely covered. Should this tissue be of the exuberant variety, however, and project above the level of the surrounding skin, the advance of this epithelial sheet is arrested, for epithelium will not grow uphill, although it apparently finds no difficulty in descending into craters on the surface.

Very extensive granulating surfaces, such as those left by the wide excision of tumors, or of the breast, often cannot be covered entirely by natural processes, or they are so slowly covered that it is not feasible to await the completion of this very tedious

process. In such instances skin grafting is resorted to in an attempt to remedy or to hasten the healing. Skin grafts are of two main varieties; one of these, the "pinch graft," consists of a thin shaving of epidermis with a little of its corium which is removed from the surface of an extremity with a special razor. It measures about a centimeter in diameter. The other variety is the "full-thickness" graft, in which a sheet of epidermis and all of its corium, with part of the subcutis, is excised from some other part of the body and sewn into place in the defect, over the bed of granulation tissue. The pinch graft is essentially a form of tissue culture in which the explant is epidermis and the medium the granulation tissue. Islands of explanted tissue are laid carefully over the granulation tissue, become vascularized, and are thus rooted to the surface. From them sheets of epidermis will grow out and cover the adjacent granulations, ultimately merging with like sheets from neighboring islands. Several of these may fail to "take," simply necrosing and remaining unattached, but there will be enough "takes" to insure the ultimate epidermalization of the wound.

There is another method of covering denuded surfaces which consists in making a flap of skin of the desired size in an adjacent region, swinging the flap over the surface, and stitching it into place without entirely detaching it from its source. The pedicle that attaches the flap to its original site continues to carry its supply of blood with it, vessels running to the flap through the pedicle. This is a "plastic graft." Sometimes the flap is made into a long cylindrical structure by cutting a long strip of skin, leaving the ends attached and sewing edges of the strip together. The bed from which this strip was taken is then closed under the cylinder, leaving the latter like a long handle. When this has healed, the "handle" may be detached at either end, swung around, split along one side and reconverted into a flat strip of skin. These pedicle grafts are much used in plastic surgery; by reason

of their length they can be swung over wide areas and portions of them used for grafting while the cylinder remains more or less intact as a conveyor of blood to the implanted graft.

Sometimes bits of skin are driven into the subcutaneous tissue by trauma and left buried there. In this case small bits of epidermis are isolated and may, by the desquamation of their keratinized layers, produce small cysts like sebaceous cysts or wens. These are known as "traumatic inclusion cysts." From them data have been collected as to the degeneration and regeneration of the dermal adnexa, already referred to above.

REGENERATION OF GLANDULAR EPITHELIUM

Unlike covering epithelium, that of the glandular structures has relatively little regenerative power after trauma, although it may exhibit considerable versatility in the

case of gastric ulcers, necrotic diseases of the liver, and so forth. In wounds of the liver the healing that takes place is usually of a cicatricial nature and there is little regeneration of the hepatic parenchyma. In certain necrotic processes, however, like acute yellow atrophy and epidemic infectious jaundice, there may be extensive regeneration. In the last named disease this is extraordinary. It is evidenced by the production of new bile ducts and capillaries and by the presence of mitotic figures in the cells of the hepatic epithelium. Although the lower mammals may show a good deal of regenerative capacity in respect to their glandular epithelium, man has apparently lost much of this. In the case of peptic ulcers, however, one frequently finds entirely healed examples that are completely epithelized. The epithelium that covers their sunken, scarred bases is practically indistinguishable from that of the surrounding and unaffected gastric mucosa.

4

General Remarks on Tumors

DEFINITION

NONMALIGNANT TUMORS

MALIGNANT TUMORS

ETIOLOGIC THEORIES

NOMENCLATURE

CLASSIFICATION

IRRADIATION OF CANCER

SENSITIVITY AND RESISTANCE OF TISSUES

THE SURGICAL PATHOLOGIST'S RÔLE IN RADIO-THERAPY

DEFINITION

The Latin word "tumor" literally means nothing more than "swelling," and while a tumor is certainly a swelling, it would be better to employ the term "neoplasm," which is derived from two Greek words meaning "new growth"; as a matter of fact, the English equivalent "new growth" is frequently used. The term "tumor," however, is so deeply rooted in medical and popular parlance that it has come to mean "new growth" and few would think of it as merely implying swelling. A frequently modified definition of a tumor is "an autonomous and localized new growth of tissue that serves no useful purpose."

Neoplasms arise from pre-existing tissue in the body by the multiplication of its cells; in this they differ radically from areas of inflammatory reaction to infection. For this reason alone one might be entitled to question an infectious origin for anything that is so fundamentally at variance with, let us say, the tubercle, gumma, or abscess. In inflammation the cells in a given focus of infection that respond to the invading organisms are almost entirely leukocytes from the circulating blood or lymph; very few cells of the tissue itself, aside from its fibroblasts and histiocytes, take part in the process. In a tumor, on the contrary, the growth is comprised of native cells, and those from the blood stream do not participate in its

formation, although they may enter it if there is a complicating infection. Naturally there are a few exceptions, as in leukemia, where the neoplasia is resident in the circulating blood and derived from one or another type of leukocyte.

There are two types of tumor: nonmalignant and malignant, or, more loosely, noncancerous and cancerous. Nonmalignant growths are often termed "benign," but the word is misleading as it implies a friendly spirit—a characterization that is quite out of place when applied to any tumor.

NONMALIGNANT TUMORS

Nonmalignant growths more or less closely resemble the tissue from which they originate; they grow slowly over a matter of years and may even regress; they are sharply defined by a capsule that encloses them in a sheath of fibrous tissue; and they do not tend to break through this to invade the surrounding tissue. Instead of seeding themselves out by metastasis (which we shall discuss presently) they remain locally active. They are not apt to be stone-hard unless they grow in bone or cartilage or become calcified. Although they may degenerate in some instances, they usually have an ample supply of blood which keeps them nourished, therefore they seldom show massive necrosis. Microscopically they are composed of well-differentiated cells that tend to resemble closely those of the parent

tissue. As these multiply slowly, mitotic figures are so few in number as to be difficult of demonstration.

From the clinical standpoint these tumors do not tend to destroy the organ in which they are found, although they may compress it or compromise its blood supply. If they arise in vital centers like the central nervous system or the mediastinum they may exert dangerous pressure on the spinal cord, brain, great vessels, trachea, or other such important structures, and even cause the death of the patient. It is also possible that they might erode bone, just as an aneurysm might. This is known as "clinical malignancy." There is a nonmalignant tumor of connective tissue known as a "desmoid" tumor which may invade muscle by infiltrating it, this is a notable exception to the rule that nonmalignant growths do not invade other tissues. This is, however, merely a local process without much pathologic significance.

MALIGNANT TUMORS

Loosely known as "cancer," from the fancied resemblance of the scirrhous carcinoma of the breast to a crawfish, these growths are quite different from the nonmalignant forms which they may superficially resemble or from which they may develop by a process that is known as "metaplasia." They grow rapidly and very seldom regress, they are poorly outlined and have no capsule worthy of the name, they invade the surrounding tissue both massively and by infiltration on the part of cells or groups of cells that wander into it from the tumor.

Malignant tumors seed themselves out by a process known as "metastasis" and thus produce daughter tumors in their vicinity or in parts far distant from them. "Metastasis" comes from two Greek words, "meta" meaning "over" or "beyond" and "stasis" meaning "stopping" or "settling." The cells settle down somewhere at a distance. Metastatic tumors then proceed to grow some times their new environment is more

favorable than the original one, and the metastases may overshadow the primary tumor from which they originated.

Many malignant tumors, particularly the carcinomas, may be stone hard in consistency. Their propensity for infiltrating neighboring tissue fixes them to that tissue so that, in contradistinction to the encapsulated and isolated nonmalignant growths, they are no longer freely movable on palpation. They are very apt to be poorly supplied with blood, as they may grow too rapidly for the blood vessels of the part. These are normal tissue and cannot grow as rapidly as the abnormal, overstimulated neoplastic cells, hence they fail to send sprouts into the newly formed tumorous tissue which, as a result, breaks down from inanition. Thus a process of necrosis invites infection and causes areas of hemorrhage into the tumor. Such hemorrhages are very prominent in the hypernephroid tumors of the kidney, for example. While a nonmalignant tumor has a resemblance to its parent tissue, the malignant variety may seem to be definitely alien.

The microscopic appearance of malignant tumors is characteristic. They may show cellular components that are fairly well differentiated and resemble those of the normal parent tissue to some extent, but as a rule this is not so. Their cells tend to be larger than normal, to have more darkly stained (hyperchromatic) nuclei, and to lack such refinements of differentiation as cilia, or mucous goblets, or other evidences of functional differentiation. Their rapid growth is evidenced by the presence of many easily found mitotic figures, many of these are apt to be of an abnormal sort. They may show very coarse and irregular chromosomes, and these may form very unorthodox equatorial plates, sometimes lining up to form a V, or producing two broad plates within two narrower ones so that there are four rows of chromosomes. They may, in some tumors, be completely jumbled into a formless group of almost spherical chromosomes. The V shaped arrangement produces

three instead of the normal pair of cells; the more abnormal groupings fail to bring about cellular division, so that huge giant cells are produced with lobated and thoroughly abnormal nuclei. These are very commonly seen in the rhabdomyosarcomas; they are known as "neoplastic giant cells," less correctly and more popularly as "tumor giant cells." Such cells are pathognomonic of malignant tumors, the only exception being the megakaryocyte of the bone marrow, which divides in a similarly untidy manner.

Malignant growths may interfere seriously with the functioning of the organ in which they grow, and they may on occasions secrete a sort of perverted imitation of the secretion of that organ; this is true of thyroid tumors and of carcinomas of the alimentary tract. They also bring about a profound toxemia by their presence, part of it due to the absorption of decomposition products set free in areas of necrosis and part of it probably attributable to something from the tumor's cells themselves, possibly in the nature of one of these perverted secretions. This accounts for much of the cachexia commonly associated with malignant growths. The presence of a large sloughing ulcerated mass in the stomach, for instance, inevitably brings about interference with the peristalsis of the organ, occludes its openings, and fills it with noxious material from the necrotic tissue.

METASTASIS

Some tumors may metastasize locally, others both locally and at a distance; we might coin the word "telemetastasis" for the second type of neoplastic spread. The mechanism is simple; observation with the slit-lamp microscope of living tumors implanted in the anterior chamber of the eye of experimental animals, or moving pictures of tissue cultures of such tumors, show that their cells are similar to leukocytes or amebae in so far as they are capable of independent locomotion. This is brought about by the extrusion of pseudopods and

the flowing of the cytoplasm into these in the manner that is familiar to anyone who has studied pond amebae. In order to obtain a more vivid idea of the activity of these cells they are photographed through a microscope onto a moving picture film in a camera that will take one frame every few minutes, instead of several in a second. The developed film is then projected at the ordinary rate of 16 frames per second and the result is to speed up imperceptible ameboid motion until it becomes clearly visible and the cell moves like an ameba. Such projections demonstrate that the cells of neoplasms may simply crawl off to another part of the body, where they divide and subdivide and create a metastatic or daughter tumor. They may also take advantage of pathways containing circulating fluids such as the blood or lymph and literally ride to their destination. It is probable that this is very indefinite and that the cells reach some point where they are arrested by the small caliber of the vessel which they then penetrate, or within which they remain to divide and produce the metastasis. The lungs are a favorite site of metastasis, and it is probable that their rich bed of small capillaries forms a sort of trap for the neoplastic cells that are migrating.

If a malignant tumor is in direct apposition with a neighboring structure, against which it is pressed or rubbed, it may inoculate this with detached cells and thus set up a subsidiary growth. This happens in the case of carcinoma on one lip inoculating the other, or carcinoma of the cervix uteri inoculating the vaginal wall, and so on. This is known as a "kissing metastasis." Carcinomas are apt to utilize the lymphatics as their route of transportation while metastasizing, spreading from chain to chain of lymph nodes by this means. Sarcomas usually metastasize via the circulating blood, although they not infrequently do so by way of the lymphatics. It is possible for tumors to metastasize along moist surfaces by having their cells detached by friction (for example, of the visceral against the parietal

pleura) and then rolled along in the fluid to some other situation. How frequently metastasis takes place by travelling along a glandular duct is problematic, but it appears to occur on occasions, as in the case of renal carcinomas metastasizing to the mucosa of the ureter or urinary bladder.

The mechanics of metastasis via the lymphatics is very important in connection with forming a decision as to surgical procedures aimed at the removal of possible early metastases together with the primary tumor. This is best illustrated by the Halsted operation for radical mastectomy, in which the breast is removed with its underlying pectoral muscles and fascia and the axillary contents are ablated. If there are any metastatic foci in these they are removed by the operation. Should the carcinoma lie in a quadrant of the breast not drained by the axillary lymphatics, this procedure would become a useless gesture, for the metastasis would then travel directly into the mediastinum, from which it might reach the lungs and brain at a later date. Thus one must know the anatomy of the lymphatic drainage of any organ upon which one is going to operate for the removal of a malignant tumor and be guided by this. It is also well to know the habitual routes of metastasis of the tumor in question, elaborate "block dissection" of lymphatic chains that are draining a sarcoma is usually almost a waste of time, as the tumor will probably metastasize by way of the blood stream.

DEGREES OF MALIGNANT CHANGE

Having defined a malignant tumor, we must consider whether this is an absolute or a relative term. Is there any difference between malignant neoplasms in respect to the degree of malignancy they may show? The answer is in the affirmative, some of the tumors are extremely malignant, being almost certain to metastasize early and widely and to kill inexorably unless they are removed at the very earliest stage of their development. Others are more leisurely

about metastasizing and are said to be "low grade."

Some years ago Broders, of the Mayo Clinic, proposed a scheme for "grading" tumors. It is based almost entirely on the microscopic appearance of the growth and depends upon the following criteria. The cells of the tumor are reviewed under the microscope and then a certain number are counted and plotted in two columns—one for the differentiated cells and the other for the undifferentiated ones. If a given tumor reveals one fourth of its cells to be poorly differentiated and the rest well developed it falls into Grade I, should it show one half of the cells in each group it is in Grade II, if three fourths of the cells are poorly differentiated it places the growth in Grade III, and if all of them show dedifferentiation it falls in Grade IV.

This scheme has its merits and its defects. Superficially it appears to be a good idea and to be feasible, but Broders added to it some qualifying factors, such as the presence of "bird's eye nuclei" and mitotic figures, indicating that it was not as simple as it seemed at first. Experience shows that there are relatively well differentiated tumors that are dangerous because of other reasons, such as a marked tendency to infiltrate. The same tumor in different situations may carry an entirely different prognosis, as the carcinoid which is nonmalignant in the appendix but may be very malignant if it occurs in the intestine. Furthermore, most pathologists do not take the time, when employing Broders' method, to make an actual count, they merely give the section a thorough going over and then estimate the percentages of differentiation and dedifferentiation. Lastly, if one takes three blocks from a tumor and makes sections and grades them, the grades may come out differently in the different blocks which represent various regions in the tumor that may be widely separated. It seems advisable, then, to make one's prognoses on a basis of a general survey of the case, including its history, to consider the type of tumor and

its reputation for malignant characteristics; and then to give a prognosis couched in plain English rather than designated by a number.

ETIOLOGY OF TUMORS

It is always discouraging to write on this subject, because thus far we have only theories to impart. Some of these are cogent, others less so. All one can do is to describe them seriatim and leave the reader to draw his own conclusions. These theories have run the gamut from the ridiculous to the reasonable, and we may be nearing a solution of the riddle which, however, has not yet been satisfactorily solved. We shall omit those that deal with the eating of tomatoes, the drinking of milk, the use of aluminum utensils, and the conversion of histiocytes into any type of neoplastic cell one encounters, and proceed with the accepted list.

Cohnheim's Theory of Fetal Rests. Many years ago Cohnheim pointed out the well-known fact that one may discover small groups of embryonal cells that remain latent in various parts of the body under normal circumstances, and he postulated that at a later time such small rests might begin to grow in response to some traumatic, physiologic, but admittedly unknown stimulus and might develop into tumors.

Ribbert's Theory of Displacements. A variant on Cohnheim's theory, proposed by Ribbert, was to the effect that groups of cells might be displaced from fetal primordia during the development of a given organ and then, in the new and alien environment to which they had been exiled, develop into tumors. Speemann's ideas concerning "organizers," or cells which act as directive agents over other cells during the development of an organ, have given Ribbert's theory some added impetus. If displaced cells without an organizer to direct their line of development were stimulated to multiply and grow they would do so in the haphazard manner characteristic of tumors.

These two theories apply chiefly to the teratoid tumors and to those well-differentiated growths that one finds displaced to

a great distance from their parent organ. Thus the finding of suprarenal tumor in an ovary, without any primary tumor elsewhere, immediately suggests that suprarenal tissue was displaced from the mesonephric primordium of the gonads and suprarenals and became attached to a gonad rather than becoming part of the suprarenal. Other similar examples could be cited, but it would take us too far afield.

Theory of Heredity. Experiments with mice, largely carried out by Tyzzer and by Maude Slye and other geneticists, attained great prominence in the early years of the century and apparently indicated that cancers were to be considered as the result of transmissible Mendelian recessive traits like albinism; the tendency toward developing a tumor would be like any other transmitted familial trait. Slye succeeded in breeding tumors into and out of a given strain of mice by employing pure strains of laboratory stock with a known history of relative immunity or susceptibility to that tumor, as the case might be. Bittner, who found that an "immune" litter when suckled by a foster mother of a "susceptible" strain would acquire her susceptibility notwithstanding their inherent immunity, seriously upset this theory and brought a qualifying factor into the picture. This is known as the "milk factor." That heredity plays a very important part in the production of tumors cannot, however, be denied; that it is the only factor seems very unlikely.

Theory of Infection. For years investigators have been periodically isolating organisms which they believed were the etiologic agents of neoplasia, only to have their discoveries disproved later on. So far as bacteria and protozoan parasites are concerned, none has stood the test of analysis; not so the viruses, which are at present in much favor. Rous first found a filter-passing virus in a sarcoma of fowls that would reproduce the tumor after being injected into other birds. He has discovered similar viruses in the "Shope papilloma," a warty lesion of wild hares. The virus is less potent,

but will produce warty lesions in rabbits as well. There is a virus that likewise evokes warty lesions on the tongues of rabbits. It must be admitted that these experiments are fairly limited to a certain sarcoma in domestic fowls and warty tumors, some of them unmistakably malignant, in hares and rabbits.

As viruses are protean in their variety, some working only in conjunction with others or with bacteria, others remaining latent until activated in some way, it is very difficult to deny that they may be an important etiologic factor. That they may apply to certain human tumors is strongly suggested by the similarity of these to those of the rabbits, but none has as yet been isolated. The ordinary epidermoid papilloma or verruca vulgaris, that of the plantar skin, and the acuminate condyloma of the anal region all suggest viral origin very strongly. That viruses are involved in such tumors as osteosarcomas, chordomas, or teratomas would seem to be much less likely.

Hormonal Theory. Out of the "chimney-sweep cancer" was born a line of research that ramifies in all directions and would make a fascinating story if expanded into book form. In 1918 and a few years later, two Japanese investigators, Yamagiwa and Ichikawa, set about painting the inner aspect of rabbits' ears three times a week with a coal tar. They knew that chimney soot would provoke dermal cancer and they also knew that long experimentation along this line had been fruitless, nevertheless they persisted in their attempts and after months of patient daubing succeeded in producing epidermoid carcinoma. Their work was repeated by several investigators, some of whom also succeeded, while others, apparently using the same methods, failed to produce cancer.

This stimulated research into the chemical nature of the tars that had been used, and Ross and Crooper, in England, found that heating coals over to temperatures in the neighborhood of 1200°C produced harmless tars, while heating to a lower tem-

perature (approximately 800°) created tars that were carcinogenic.

The matter of determining which fractions of these distillates possessed the carcinogenic properties was ably taken in hand by Kennaway of the Royal Cancer Hospital in London. He hit upon the expedient of synthesizing various oils from isoprene and testing them out on animals. They were carcinogenic but very complex, and the isolating of various fractions from these and the carrying out of biological tests with each were equally time consuming. Kennaway's collaborators Hieger and Mayneord conceived the idea of using a spectroscope to predict carcinogenicity; they had observed that the tumor-producing tars became fluorescent in ultraviolet light and that their spectra showed three characteristic absorption bands. Thus they empirically discarded any fractions that failed to show these and their premonitions were found to be well founded. It was soon found that the carcinogenic tars were of the type of the derivatives of anthracene. Various dibenzanthracenes were found to vary in their potency, some being weakly active while others were strongly so, 1-2,5,6-dibenzanthracene was one of the latter.

In this country Fieser investigated these substances and found wide variations in potency resulting from the rearrangement of the molecules. The shifting of one side-chain from one position to another in the molecular framework might render a virulent carcinogen quite harmless. These substances, synthesized in crystalline form, were found to produce a variety of tumors depending upon the site of their injection, and much experimental work immediately ensued upon their discovery. An important feature of the anthracene group is its sterol nucleus. Cholesterol has always been bobbing up in connection with cancer research; one will find it mentioned as far back as 1911. Now it has become doubly interesting. The discovery of methyl cholanthrene furnished a link between all this theoretical chemistry and the normal chemistry of the

body, for this substance may be synthesized from cholic or desoxycholic acids, normal constituents of the bile, and it is one of the most powerful carcinogens. Chemical analysis of the hormones and of vitamin D had proved these, too, to be sterols.

Cook and Dodds were successful in producing estrogenic substances from some of the carcinogenic coal tars. Next a group of investigators proved that the estrogens would produce tumors when injected into animals, thus in a way reversing the process. A great many investigators have continued to expand this work, and here the matter rests for a while, but it provides ample stimulation for conjecture.

Carcinogenic chemicals do not all belong to the group of sterols and there are many that are quite foreign to it. Betanaphthylamin has been employed because of the occurrence of carcinoma of the bladder in workers in aniline factories. The dyes "butter yellow," Biebrich's scarlet, and derivatives of quinoline have all proved to be more or less carcinogenic. Other much simpler substances, such as zinc chloride, have shown these properties. The important factor in evaluating this work is the question as to whether the given chemical is one that might conceivably be synthesized in the course of human metabolism in the human body.

The so-called cancer age and the period of sexual involution coincide in the "roaring forties" and onward; the development of tumors in children occurs at the age of puberty and adolescence. These coincidences have the appearance of depending upon a common etiology, although this might be a fallacy.

Combined Theories. It is quite possible that there is some validity in all of these theories and that no one of them would account for the occurrence of every type of tumor. It appears as though a combination of the proper heredity and the proper latent stimulus (whether viral or hormonal) with something to set off this explosive combination might come fairly close to explain-

ing the mechanism of carcinogenesis. That this "detonator" is trauma has long been maintained, but of late less and less weight is credited to it. That it is a brief and acute form of trauma is seriously considered only in the courts of law; chronic inflammation or irritation has more to be said in its favor. We know that long exposure to sunlight or the x-ray can produce dermal cancer and that cancer of the lip may follow the smoking of hot clay pipes or the mumbling of hot cigar stubs. As women develop cancer most frequently in the two organs most traumatized during the production of a child, the uterus and breast, one cannot avoid drawing conclusions even if the present vogue points away from any connection between the trauma and the tumor.

NOMENCLATURE OF TUMORS

There are two fundamental methods for naming tumors, one of them based upon histology and the other on histogenesis. The former has a limited scope, as it will not apply to any but the nonmalignant tumors which closely imitate normal tissue. In their case one is forced to fall back upon the second method by deducing the probable origin of the cellular components of the tumor in question. Even this may fail us, for malignant tumors may become so dedifferentiated as to present no clearly recognizable features; then refuge is taken in applying the morphologic method employed before much thought was given to histogenesis. In this the shape of the cell is all one has to go by and, accordingly, such tumors are spoken of as being "round-celled," "spindle-celled," "oat-celled" and so on. This has the manifest disadvantage of giving no clue as to the probable origin of the growth, and it is usually an admission of partial defeat in diagnosis. This is partial because, after all, one may recognize the malignant quality of the growth and warn the surgeon accordingly, and this is all that interests the more materially minded physicians, who care little about the origin of a growth. One should use this method, however, only when

one is forced to, no conscientious pathologist can feel at peace with himself when he cannot give the fullest possible information concerning a tumor

There are a few growths that are named after the organ in which they occur, but these are becoming less and less numerous, this is often an unnecessary procedure and should be employed as sparingly as the morphologic type of nomenclature. It comes into play when the histogenesis of the organ in which a tumor arises is itself of a doubtful quality. For example, the thymomas were so called because of a dispute among histologists and embryologists as to the origin of the lymphocytic cells in that organ. The question as to whether they were lymphocytes that had migrated into the thymus during its embryonic development or whether they were "small thymocytes" derived from the ectodermal thymic reticulum was unsettled, and until it was decided it seemed better to call tumors composed of these cells "thymomas."

There is one more type of nomenclature that rests upon a similar foundation, and this is the eponymic type that applies the name of some pathologist or surgeon to the tumor he has been the first to describe. Thus we have "Ewing's tumor of bone," "Brenner's tumor of the ovary," the "Krukenberg tumor of the ovary," and several other such appellations. In the case of Ewing's tumor the name is still used because it expresses a growth of still definitely undetermined origin and concerning which there is continuing dispute. This is not true of the Brenner and Krukenberg tumors, which are now well understood.

Histologic Nomenclature As every tumor is made up of cells derived from some tissue it was attempted to classify them by naming them after that tissue. Frank Mallory used to speak of "type cells," which is a useful if somewhat inelegant term to say "typical cells" or "typifying cells" might be more correct, but it would be clumsy and less forthright in its effect. For that reason "type cells" will figure

throughout this book. The type cell of the fibrous tissue is the fibrocyte, that of the muscular tissue the myocyte, and so on, by adding the ending "oma" to this one expresses the idea of a tumor composed of these cells. Thus we get "fibroma," "myoma," "chondroma," and a host of other "omas." This well expresses a nonmalignant tumor originating in these tissues. A tumor that combines both fibrous and muscular elements, such as the fibrocyte and the myocyte, would be a fibromyoma. So far so good, but when we come to epithelium we have to deal with covering and with glandular varieties, which complicate matters. To call such tumors "epitheliomas" would be misleading, for one would not know whether covering or glandular epithelium was implied in the name.

"Epithelioma" should mean an epithelial tumor, but it was for so long a time used to denote "epidermoid carcinoma" that there is still confusion when it is employed for nonmalignant tumors of that tissue. Most nonmalignant tumors of the covering epithelium are papillary, so that the name "papilloma" has arbitrarily been applied to them, although one may say "papillary epithelioma" with equal propriety. Unfortunately the term is also applied to papillary growths of glandular ducts, but ambiguity can usually be overcome by adding qualifying adjectives like "intraductile," or adding the name of the organ in which they occur, as "papilloma of the ureter." For the tumors of glandular epithelium the name "adenoma" (tumor of gland) has been adopted.

Histogenetic Nomenclature A number of pathologists attempted to introduce the addition of "blastoma" to a tumor that exhibited embryonal, metaplastic, and malignant traits in order to distinguish it from its nonmalignant relatives. Thus the type cell of a malignant fibrous tumor was the "fibroblast," that of the malignant myomas the "myoblast," and so on. This is an excellent plan, but it has failed to take root because physicians and scientists in general were used to calling malignant epithelial

body, for this substance may be synthesized from cholic or desoxycholic acids, normal constituents of the bile, and it is one of the most powerful carcinogens. Chemical analysis of the hormones and of vitamin D had proved these, too, to be sterols.

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arrive at a prognosis and predict their susceptibility to treatment. Again to illustrate, let us take the appendiceal carcinoid. In the appendix, classified by its association with that organ, it is innocent in almost every instance. As a tumor of the alimentary tract, on the other hand, we know that it is frequently malignant when it arises in the jejunum. As a member of another group of tumors classified by their staining characteristics (which we shall not explain here) it should exhibit granules which impregnate with silver, this serves to identify it beyond all doubt. As it is derived from nervous elements and can be classified another way as a part of the nervous system, it should, like that system, be insensitive to irradiation with the x ray—and it is.

In the pages that follow the reader will be able to grasp the significance of classification, sometimes it will appear quite frankly and openly, while at other times it will be implied. Without some adherence to its principles a book could scarcely be written, as it forms an underlying framework upon which to erect the descriptive material that serves to make the subject comprehensible and clear.

IRRADIATION OF CANCER

During the past twenty years tumors have been treated with increasing frequency by irradiation with radium or its emanation or by the x ray. At first this gave promise of great results, but as time has passed it has been found to be disappointing, and its application has been limited to certain growths.

Radium. When radium is used, the destructive power of all three of its rays, the alpha, beta, and gamma, are brought to bear upon the irradiated tissue. The emanation of radium, in a gaseous form that gives off gamma rays, has taken its place in practice. This is because of the prohibitive cost and limited supply of radium and because its emanations are constantly given off from the stock supply and may be stored in small gold bomb like "radon seeds" with which

its action can be much more accurately controlled. The seeds ultimately emit all their stored emanation and become inert, while the radium continues active almost indefinitely and must be retrieved from the patient when it has accomplished its purpose. Otherwise it becomes a menace.

Each radon seed (which measures about 3 mm in length and 2 mm in diameter) may be inserted into a tumor and will exert a destructive effect throughout a volume of the tissue that surrounds it equivalent to that of a sphere with a diameter of 1 cm. By so planting the seeds that their spheres of action overlap slightly, an entire tumor may be irradiated and destroyed. They may be introduced through a sharp cannula thrust into the growth, being pushed out of this into the tissue by means of a trocar. Sometimes a group of cannulae in a "gang" is used, several cannulae being thrust simultaneously deeply into the tumor, the instrument is then withdrawn one centimeter and another series of seeds planted in the tissue. This is repeated until the cannulae are completely withdrawn and a large number of seeds, with overlapping spheres of action, have been deposited in the growth.

X rays. The x rays are directed at the tumor through "ports," which are not unlike nozzles and may be large or small, producing wide or very limited lanes of entrance for the rays. Or the exposure may be of the "spray" or generalized variety, when large areas of the body are to be irradiated. The treatment may be directed toward two ends. Advantage is sometimes taken of its caustic or coagulating action in connection with superficial growths that are known to be resistant to the x ray, or this may be filtered so as to approximate the gamma rays of radium. A 900 kilovolt tube with proper filtering of the x rays through copper and aluminum plates will produce this effect, but the most powerful machines seldom exceed 700 k. V. on account of the destructive effect of such high currents upon the tubes.

growths "carcinomas" (from the Greek *karkinos*, crawfish) and those of most of the other tissues "sarcomas" (Greek *sarx*, flesh). A compromise was effected by adding to the stem-syllable of the type-cell the affix "carcinoma" or "sarcoma," or by adding one of these to one of the qualifying stems like "adeno-." This results in the production of words like "adenocarcinoma," "myxosarcoma," and the like. Sometimes adjectives are used outright, as in "epidermoid carcinoma" (a carcinoma resembling epidermis). Strict adherence to the method of affixing "blastoma" in the case of epithelial growths would give us cumbersome and inexpressive terms like "epithelioblastoma," and as most of the malignant tumors arise in epithelium this would lead to much confusion as well.

Compound Terms. There is much to be said for a descriptive name, and merely calling a tumor of glandular origin an "adenoma" would not be descriptive at all, beyond indicating that the growth was of glandular parentage. Therefore we modify the term by prefixes and adjectives. A cystic adenoma becomes a "cystadenoma"; if it is papillary to boot it is called a "papillary cystadenoma" or a "cystadenopapilloma," which verges on the imposing or pompous side. A sarcoma exhibiting elements typical of the development of bone might be called a "fibrochondrosteosarcoma," which would make one word express a good deal, but again it is too mouth-filling, and "osteogenic sarcoma" (if one has studied the matter a little) answers very well. One should always strive to use as simple an expression as possible, for the idea is to enlighten and not to confuse the user of the report. For this reason it is better to speak of a "canalicular adenofibroma" than of a "papillary intracanalicular adenofibromyxoma."

CLASSIFICATION

A convenient method of classification is as necessary for tumors as it is for birds or flowers or inorganic chemicals; one must know something of their relationship to the

organs and tissues in which they are found. This facilitates descriptions in books or in teaching, and it makes the subject much more comprehensible. New growths that arise in widespread tissues like fibrous, adipose, osseous, or other connective tissue are best classified in connection with these. Those that are found in organs in which the epithelium or other tissue is somewhat locally specialized, like the liver, stomach, kidney, and the like, are best classified with those organs; like the organ in which they are found to arise they have characteristic distinctions in common with that structure.

To illustrate this let us take the breast. This is composed of intrinsic functional elements and extrinsic supportive structures. The mammary gland and nipple contain ducts, canaliculi, and acini that have their own peculiar tumors. The covering mucosa of the nipple also presents some neoplasms that are peculiar to it. The extrinsic, supportive tissues, however, show no tumors that could not be found elsewhere in the body, such as lipomas, fibrosarcomas, angiomas, tumors of the nerves, and so on. If we group the tumors actually found in any given organ (or of a type that might be found there) into a schema based upon the anatomy and histology of that organ, we shall have a systematic outline of all the tumors that might be encountered. Some of them, like rare elements in a table of atomic weights, may be for the present hypothetical, but categories have been provided for them should they at some future time turn up in the laboratory. As an illustration, we are prepared to find nonmalignant lymphomas, retiotheliomas (reticulum-celled tumors that are nonmalignant), malignant tumors of the neuromyo-arterial glomi, and probably a few others, although they have not as yet been definitely accepted as entities.

A great many new growths may be classified both by systems and by organs, and by utilizing our knowledge of their behavior in a given organ as opposed to their characteristics as exhibited in a given system we can

OTHER FACTORS IN SENSITIVITY AND RESISTANCE Besides fibrosis, inflammation as a result of infection together with an anemic state of the circulating blood in a tumor will increase its resistance. Radiotherapists shy away from treating large sloughing tumors for this reason. After irradiation there is an increase in the number of lymphocytes and plasma cells in the treated area, these have been supposed to be antagonistic to neoplastic cells. This phenomenon is also noted in areas of absorption of surplus, unwanted tissue in the developing embryo. Irradiated areas also undergo fibrosis, but if the fibrous tissue is poor in vessels there is apt to be a survival of some of the neoplastic cells. Some tumors, such as the lymphosarcoma, appear to be destroyed by the direct action of the x-rays, others are adversely affected by the sclerosis resulting from irradiative trauma, still others may disappear because of the inactivation of an organ that controls their growth, as the leiomyosarcoma does after the ovaries have been irradiated. This last effect is known as "indirect therapy." Many tumors that are only moderately susceptible to irradiation, but which are very vascular, will respond to x-rays because of the destructive effect upon their vascular supply. This is particularly the case in those tumors which contain many "true papillae," which are chiefly composed of capillaries covered with the neoplastic cells. In these the thrombi that are produced bring about necrosis. Conversely, tumors that are heavily keratinized are very resistant.

There has been frequent mention in the preceding paragraphs of necrosis, necrosis with hemorrhage, thrombosis, coagulation necrosis, and the like. This implies the setting free of split proteins in the body and suggests that the patient may react unfavorably to them. This is the case, and some patients declare that they would rather die of the tumor than go through with the nausea and diarrhea occasioned by the treatment. Others take it with more equanimity. X irradiation is a dangerous and unwar-

ranted method of therapy in any but the most experienced hands. Not only does x-ray cure or improve some tumors, but it can produce them if given time. In the early days of roentgenology, before the operators were protected by lead from the action of the rays, many of them lost fingers, hands and ultimately their lives through the development of epidermoid carcinoma.

THE SURGICAL PATHOLOGIST AND X-RAY THERAPY After having diagnosed a tumor as malignant, the pathologist is frequently asked by the surgeon if the growth will be susceptible to x-irradiation. The answer is always rather tentative. The above outline gives the theoretical side of the matter, but in practice it will be found that tumors do not always respond as they theoretically should. For example, the neurogenous sarcoma may be very delicate, very vascular, and studded with mitotic figures, but these apparent indications for the advantageous use of radiotherapy are all cancelled by the fact that the growth is neurogenous and hence highly radioresistant. The use of x-irradiation in conjunction with surgery was formerly advised on very slight provocation. Irradiation of a tumor before operation usually results in fibrosis and leaves the surgeon with a field of operation that is tough and leathery. All cleavage planes have been amalgamated, the vessels gape open and will not retract or close, furthermore they are hard to clamp in the surrounding fibrous tissue. Healing is definitely retarded. Therefore if irradiation is to be advised in conjunction with surgical operation it should not precede the operation, but should follow it at a decent interval, after the wound has begun to heal to such an extent that the completion of the process will not be interfered with. Lastly, there is a good deal of mutilation after x-ray treatment. The skin shows unsightly purple scars that last for a long time, and the growth of fibrous tissue in the path taken by the rays may bring about stricture of neighboring loops of intestine or similar effects that will require further operative procedures.

ACTION OF X-RAYS. As a primary effect these initiate changes in the thin-walled vessels of the body, causing desquamation of their endothelium with consequent thrombosis. This produces infarcts in the tumor with resulting necrosis and hemorrhage, or simply coagulation necrosis. Tumors that are not particularly well supplied with thin-walled vessels, however, may be made to disappear through the apparently combined action of the x-ray upon the neoplastic cells and the bed of tissue ("tumor bed") in which they lie. Fernau, quoted by Stewart, whose monograph serves as a basis for this brief discussion, believes that the following factors may be responsible for the action of the rays. There is injury to the vessels, damage to the limiting membranes of the neoplastic cells, and increased permeability of the vascular walls and these cellular membranes. With this there is a change in the pH and in the osmotic pressure of the irradiated part, changes in the rate of diffusion between the blood and the tissue, flocculation of albumin-lipid combinations, and an alteration in the rate of oxidation, with disturbances of chemical processes. With all these out of joint it is small wonder that the tumor suffers!

SENSITIVITY OF TISSUES TO X-RAYS. Desjardins experimented with the sensitivity of various fundamental tissues in the normal organism to the action of the x-ray and found that they were affected according to the following descending scale. The lymphocytes are the most sensitive, the nervous tissue the most resistant.

1. Lymphoid tissue and lymphocytes.
2. Neutrophil and eosinophil polymorphonuclear leukocytes.
3. Epithelium (again in a descending scale):
 - a. Basal salivary epithelium.
 - b. Basal testicular and ovarian cells (spermatogonia and follicular cells).
 - c. Dermal and mucosal epithelium of some organs such as the stomach and intestines.

d. Pulmonary alveolar epithelium, bile-duct epithelium.

e. Renal tubular epithelium.

4. Vascular endothelium and peritoneal and pleural mesothelium.
5. Connective tissue.
6. Muscle.
7. Bone.
8. Nervous tissue.

From this it will be seen that as cellular differentiation increases, resistance of the cell to the action of the x-ray increases with it. Very fibrous tumors tend to be radio-resistant, and a glance at the position of fibrous connective tissue in the above list explains this. Radiosensitivity depends upon the delicate structure of the tissue, a healthy vascular supply with a circulation of normal blood, active metabolism and, finally, the presence of much mitotic activity.

DOSAGE. The amount of x-ray therapy to be applied in a given case is a matter for the expert, and no one who is not familiar with it should attempt to administer x-ray therapy. The dosage varies with the individual, the type of tumor to be treated, and many other factors. It is not proportional to the effect; 300 to 400 R. (roentgen units) will produce 50 per cent mortality in the freshly deposited eggs of drosophila, the fruit fly; after these have developed as far as the gastrula stage, however, 1,200 to 2,000 R. will be required, as the cells are more differentiated and hence less sensitive. Rapidly growing tissue with many mitotic figures present is more sensitive to the x-ray than is slowly growing tissue. Some areas of a Flexner rat-sarcoma will be killed by 200 R., while it requires 2,200 to destroy the entire tumor.

The reader may be curious to know the definition of an "R." One R. is the amount of x-irradiation that the associated corpuscular emission will produce in 0.001293 Gm. of air ions carrying one electrostatic unit of charge of either sign. It will be seen that the calibration of a therapeutic x-ray apparatus is not child's play!

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The miraculous disappearance of lymphoid tumors after irradiation gave great promise, but a follow-up investigation has usually proved that they have recurred after a few months and have to be treated again. After a few such repetitions the tumor becomes increasingly radio-resistant. This is also true in the case of Hodgkin's disease. The treatment of carcinoma of the cervix uteri by radium stands out as one of the almost certain triumphs in this field; the application of radium therapy to these tumors effects complete disappearance of the growth in many instances without any surgical intervention.

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ever it may be located, and in the loose areolar tissue of the subcutaneous variety, or that found in organs, it is common in the walls of vessels. Such membranes as the leptomeninges contain a great deal of it. It is difficult to stain reticulin, the element of reticulum, with dyes so that it may be recognized, but it becomes jet black with deposited metallic silver in impregnations.

Inflammation of Connective Tissue Inflammation in the connective tissue, whatever may be its type, is essentially the same in any case. This group of tissues is very resistant to inflammation, as may readily be proved by the examination of gangrenous extremities or organs. The connective tissue is the last element to succumb to the process, and indeed it may even be formed in the face of intense inflammation. It is produced in large quantities in some forms of chronic inflammation, the term "fibrous" being very often encountered in conjunction with "chronic inflammation": fibrous cholecystitis, fibrous appendicitis, fibrous pleuritis, and the like.

There are several groups of diseases characterized by changes in the fibrous tissue, notably the rheumatic and rheumatoid affections and the group of vascular diseases that have recently come into prominence and have been discussed in connection with the chapter on vascular diseases. Disseminated lupus erythematosus is one of these that not only exhibits fibrous proliferation but presents a peculiar form of this known as "fibrinoid degeneration," in which there is a hyaline change in the collagen with the formation of laminae separated by spaces and resembling the layers of an onion. Embedded in these laminae are droplets of a hyaline material that has the staining properties of fibrin, hence the term "fibrinoid."

In scleroderma there is a widespread and devastating development of dense connective tissue in the derma and in various organs. It may invade and destroy muscular bundles and bring about atrophy of organs. Whether this be primary in the connective

tissue or secondary to some other stimulus is debatable.

Tumors of Connective Tissue The tumors of any group of connective tissue are more spectacular than its inflammatory reactions, but one must be careful to keep those changes that are due to inflammatory stimuli sharply differentiated from those that represent genuine neoplasia.

Keloid In some people, notably Negroes, there is a tendency for an overgrowth of collagenous tissue when scars are formed after injury, instead of a wound presenting enough connective tissue to hold the edges together and fill the defects, collagen is produced in superabundance and the wound becomes heaped over with protruding knobs and masses of dense, leathery scar tissue. The Polynesian tribes utilize this to produce intricate designs upon the skin of the face, torso, and arms by simply creating a pattern of incisions that are forced to heal slowly and to create hyperfibrosis that brings out this pattern in permanent bas-relief. Keloids go the exuberant scar one better by forming actual tumor-like masses in and under the skin. A simple needle puncture in a baby's ear lobe for the purpose of accommodating future earrings very often gives rise to a small, spherical, firm tumor a centimeter or more in diameter, we all see them sooner or later in the dispensaries. A series of boils on the nape of the neck will call forth a series of rubbery excrescences that are most unsightly. An extensive burn of the skin will cause horrible disfigurement.

Under the microscope these "tumors" closely resemble ordinary fibrous scar tissue, the collagen they contain is hyaline, and the individual fibrils are swollen and coarser than those of a true neoplasm. The skin that covers the growth shows no dermal adnexa such as hair follicles or sebaceous glands. The keloid is extremely acellular, and few nuclei are to be noted. It presents problems in therapeutics, as the very thing that causes it will have to be employed to remove it surgically. Careful removal and

5

Fibrous Connective Tissue

TYPES

COLLAGENOUS

ELASTIC

RETICULAR

INFLAMMATION

TUMORS

FASCIA, TENDONS, AND LIGAMENTS

INFLAMMATION

TUMORS

This is ubiquitous in the human body and consists of three distinct types. The bulk of it is collagenous, the rest of it is either elastic tissue or the reticular type known as "reticulo-endothelial tissue."

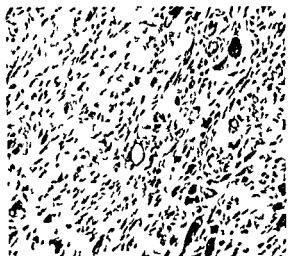
Collagenous Tissue. Fibroblasts or fibrocytes, as they are sometimes called, are invariably associated with the collagenous fibers that constitute this tissue; it is probably the least differentiated and most resistant tissue of the body in respect to both its cellular and its fibrous elements. The cells are embedded in a mass of thickly matted strands of collagenous fibers which may be produced by the action of secretions from the fibroblasts upon fluids in the tissue as a sort of precipitation phenomenon. They are white, very strong, nonelastic and do not tend to stretch. They constitute the fundamental connective tissue of the body as a whole, holding its various components together, and as a result this tissue is found everywhere; even the transparent cornea is a form of collagenous tissue covered by epithelium. Its fibers are stained red by eosin or by acid fuchsin, blue by aniline blue, rusty brown by phosphotungstic-acid hematoxylin, and green by "light green" (in the Masson technic); in silver impregnations they impregnate a magenta of varying intensity.

Elastic Tissue. This, too, is apparently produced by the action of fibroblasts, for one never hears of "elastoblasts" or is con-

scious of having seen such cells. It differs from collagenous tissue in being easily stretched and elastic in the sense that rubber is elastic; its color is yellow rather than white, and it is found in situations where elasticity is necessary: walls of arteries, subcutaneous tissue, sheaths or capsules of glands, and glandular tubules or ducts. It stains red with eosin, acid fuchsin, ponceau, and phosphotungstic-acid hematoxylin: purple to black with the special stains of Weigert and Verhoeff. In the Masson technic it is readily recognized, as it takes the red ponceau and not the light green dye.

Reticular Tissue. This tissue is the product of the "cell of many aliases," the reticulo-endothelial cell or histiocyte. It is much less compact than the two preceding types of tissue and is formed of delicate argyrophil fibers that are arranged in a network that is loosely meshed; hence the name "reticulum" or "reticular tissue." There has been considerable dispute as to whether reticulum and collagen are distinctly different chemical substances or merely somewhat different physiochemical phases of the same chemical entity. It seems probable that reticulum may be in the nature of a chemical substitution product of collagen, containing a group with hydrogen atoms, and of phosphorus, which is lacking in collagen. This has been discussed elsewhere in this book. The reticular tissue forms a framework for the lymphoid tissue, wher-

turer forms of the tumor these are replaced by collagenous fibers. It does not seem certain that this indicates that the reticulum is bound, given due time, to be converted into collagen, but it seems empirically true that reticulum is more usually found in the more malignant and rapidly growing fibrosarcomas, collagen in the less malignant and more leisurely examples. A fibrosarcoma that shows a very marked tendency for its



Fibrosarcoma of the back. In spite of its very malignant appearance the tumor has been relatively slow growing although it has recurred repeatedly. Patient has survived for five years.

component cells to become grouped into interlacing bundles and exhibits little collagenous matrix is always suggestive of neurogenous origin, being derived from the connective tissue of the neural sheaths. When a fibrosarcoma invades bone it often provokes a reaction on the part of the osteoblasts that result in a misleading picture which may be taken for that of osteosarcoma, one must always be on the lookout for such mistakes when fibrosarcomas arise near bony structures.

RETICULUM CELL TUMORS These are fully discussed in the section on tumors of the lymphoid organs.

FASCIA, TENDONS, AND LIGAMENTS

These tissues are an integral part of the locomotive apparatus and are almost as

ubiquitous as is connective tissue itself. They are seldom the site of acute inflammation, as they are composed of very dense, inert, and resistant tissue that is not easily inflamed. In the case of the tendons, however, inflammation of their sheaths is another matter, as these spaces lined with mesothelium afford splendid lanes for the spread of infection and become readily inflamed after they have been penetrated and inoculated with infectious material.

Chronic Inflammation Chronic inflammation of ligaments and tendons is known among orthopedists as "desmositis" (from the Greek "desmon," a ligament). It is often associated with rheumatic and gouty conditions or it may be attributable to other causes.

DUPUYTREN'S CONTRACTURE The palmar fascia is the site of a strange, progressive thickening and fibrosis in some patients, as a result of this the leaf that runs to the fourth or ring finger becomes nodular and contracts until the finger is permanently flexed into the palm of the hand and cannot be extended even to its normal mid position. In early cases this thickening may be felt as a relatively small nodule in the palmar fascia, and the deformity may go no further than that. It has a definitely familial occurrence in some instances, for example, a personally observed family presented two brothers and a sister in whom the contracture developed in later life. It occurred in the next generation in the son of another sister who had not developed it and in two sons and a daughter of the affected sister. One of the brothers died childless, the other had two children, one of whom died in early childhood and the other, a female, did not develop the lesion. There is a marked incidence of rheumatoid arthritis in this family. With such a startling coincidence of occurrence in the members of two generations of one family, together with the presence of rheumatoid arthritis, the evidence that the deformity is familial is very strong, but whether this depends upon heredity or

after-care of the surgical wound will usually result in a "cure."

FIBROMA. There are two classical types of fibroma: the hard and the soft ("durum" and "molle" in Latin). The former is composed of dense connective tissue that varies in its cellularity. Macroscopically the tumor is hard, fibrous looking, and spheroidal, and it is well encapsulated and demarcated from



Desmoid variety of fibroma, showing a very cellular area with much coarse fibrous collagenous tissue. As this stains light green by Masson technic, it photographs almost white.

the surrounding tissue. Histologically the picture varies from one of marked cellularity, with bands of fibrocytes forming bundles and embedded in collagenous fibers, to one in which there is little else than dense collagenous tissue with very few visible fibroblasts. These are inconspicuously compressed into small spaces in the fibrous felting. There is a definite group of fibromas that shows a very intricate, curly arrangement of its fibrils which appear to radiate from innumerable centers and give the microscopic picture a decidedly stellate arrangement. Such tumors are usually attributed to an overgrowth of fibrous elements of nerve sheath and are therefore called "neurogenic" or "neurogenous" fibromas. Nerves may pass around them or enter them. As will be seen in the chapters on the

various systems, almost no organ is immune from fibrous tumors which are particularly common in the ovary, kidney, and integument.

The soft fibroma is usually subcutaneous and springs from the skin by a pedicle, hanging down like a wrinkled and very unsightly bag. Grossly it cannot be differentiated from the lipoma of similar external appearance until it is exposed at operation and fat is or is not demonstrable on section. It may accompany the neurofibroma and lipoma in von Recklinghausen's multiple neurofibromatosis. Microscopically it is found to be loosely constructed and edematous and often to contain large numbers of elastic fibers which escape notice in sections stained with hematoxylin and eosin, but which stand out prominently in stains that are more selective, like the Masson technic. This probably depends upon the fact that the elastic layers of the corium are involved in this superficial type of tumor. Whatever may be the reason for this peculiarity, this tumor is the nearest approach to an "elastic fibroma" that one ever observes; a separate paragraph on tumors of the elastic tissue, therefore, would be ridiculous.

FIBROSARCOMA. Fibrosarcoma resembles fibroma in its gross appearance, but differs from it in its great rapidity of growth, its greater size, and its tendency to invade neighboring tissue, including bone. It is not sharply demarcated, but fades imperceptibly into its surroundings. Microscopically the type-cell may vary from a fairly well-differentiated fibroblast to a travesty of that cell that is many times its normal size and possibly multinucleated. The nuclei are hyperchromatic and may be lobulated. This tumor is much more cellular than is the fibroma, and it usually forms comparatively little collagenous tissue, the growth consisting of closely set and atypical fibroblasts that tend to run in groups that form interlacing or parallel bundles of cells. One may usually demonstrate reticulum scattered all through these cellular bundles in sections that have been impregnated with silver; in the ma-

nized, have been described briefly under the granulomas in the chapter on inflammation. Surgeons may excise them for biopsy purposes, or the younger men in the surgical clinic may excise them in the mistaken belief that they are fibromas, from which they differ slightly in their gross appearance, microscopically there are more definite points of differentiation.

Heberden's Nodes These were described by Heberden in his Commentaries, published in 1802. It is noteworthy that his description has not been improved upon in the succeeding years. He called them "small tumours, about the size of a pea, which sometimes form near the third joint of the fingers." He remarked that they were "rather disfiguring than inconvenient, although the movements of the fingers are somewhat hindered by them." They combine bony outgrowth with small cystic swellings that contain a glairy fluid, possibly they are herniations of the synovial membrane. They occur in connection with osteo arthritis and may be sufficiently painful or tingling to interfere with the finer movements. Heberden denied that they had any connection with gout. Their microscopic appearance is unimportant.

Rheumatoid Juxta articular Nodules These have been described at length in the chapter on inflammation, under the granulomas.

Tophi of Gout These, too, are described elsewhere in connection with the arthritides.

CALCIFICATION Aside from calcific nodes near tendons, there is a process of progressive calcification of the insertion of tendons of some muscles, such as those of the adductor group of the thigh. This may produce spurs of bone as the salts of lime gradually undergo organization and ossification. A good example of such calcification is the "rider's spur" that develops on the inner side of the knee in the tendon of the adductors and is supposed to result from the constant irritation incidental to gripping a

saddle with the knees. Microscopically these spurs show little of great interest unless they are associated with some of the osteosarcomas (qv), they occupy a position midway between that of the lesions of tendons and of the exostoses.

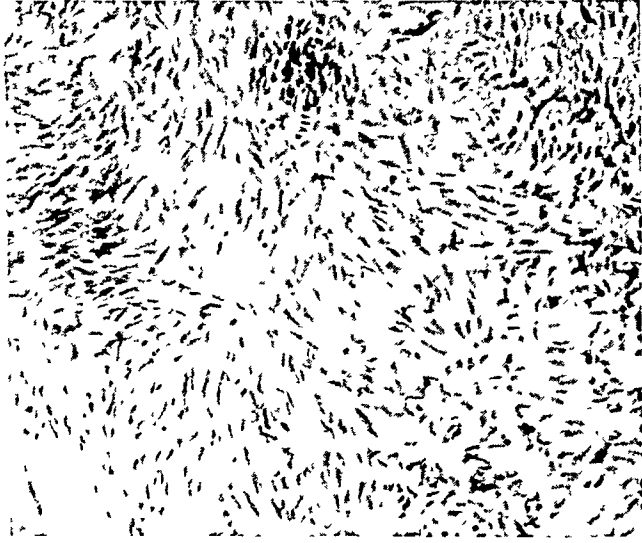


Typical juxta articular nodule in rheumatoid arthritis. It shows a few giant cells and as yet no necrosis. (Army Medical Museum 64903.)

Tumors of Tendinous and Fascial Tissue On account of their intimate relationship with the bone, tendons may share with that tissue in the possession of certain tumors that arise in the periosteum. Fibromas, fibrosarcomas of the periosteal type, and chondromas may be observed. Fascial sarcomas are apt to be associated with mucoid degeneration and thus may produce myxosarcomas. One of the most interesting tumors of the fascia is the fascial liposarcoma in which fibrous, adipose, and mucoid connective tissue all share in the formation of the growth. It has been described under "lipoma."

upon a susceptibility to rheumatoid arthritis is not clear. The contractures are very common in "rheumatic" people.

After such a contracture is excised it proves very disappointing when examined. It presents a small oblong of nodular tendinous tissue that is definitely thickened and slightly pinker than normal. Microscopic examination reveals at most an overabundant supply of fibroblasts, occasionally



Area of fibroblastic proliferation at center of a nodule in Dupuytren's contracture of palmar fascia. This is the only discoverable feature of the lesion, which is otherwise made up of inert collagenous fibrous material.

perivascular sleeves of lymphocytic or plasmocytic exudate, and an inert mass of collagenous connective tissue. The finding of perivascular inflammation is very exceptional.

PEYRONIE'S DISEASE. There is a nodular fibrous thickening of the fascia over the dorsum of the penis that is analogous to Dupuytren's contracture and sometimes occurs in conjunction with it in the same patient. This was first described by de la Peyronie in the latter half of the eighteenth century and has gone under the name of "Peyronie's disease" since that time, also being known as "penile strabismus" or less elegantly as "squint of the cock." It consists of the appearance of a nodular thickening

that contracts the dorsal fascia, pulling the penis out of line during erection and causing it to deviate to one side or the other, at the same time curving in an angulated fashion. The contracted and thickened band is usually about 3 cm. in length and a few millimeters in width and thickness. It lies over the connective tissue that separates the corpora cavernosa in the dorsal groove between them. Its cause is quite unknown.

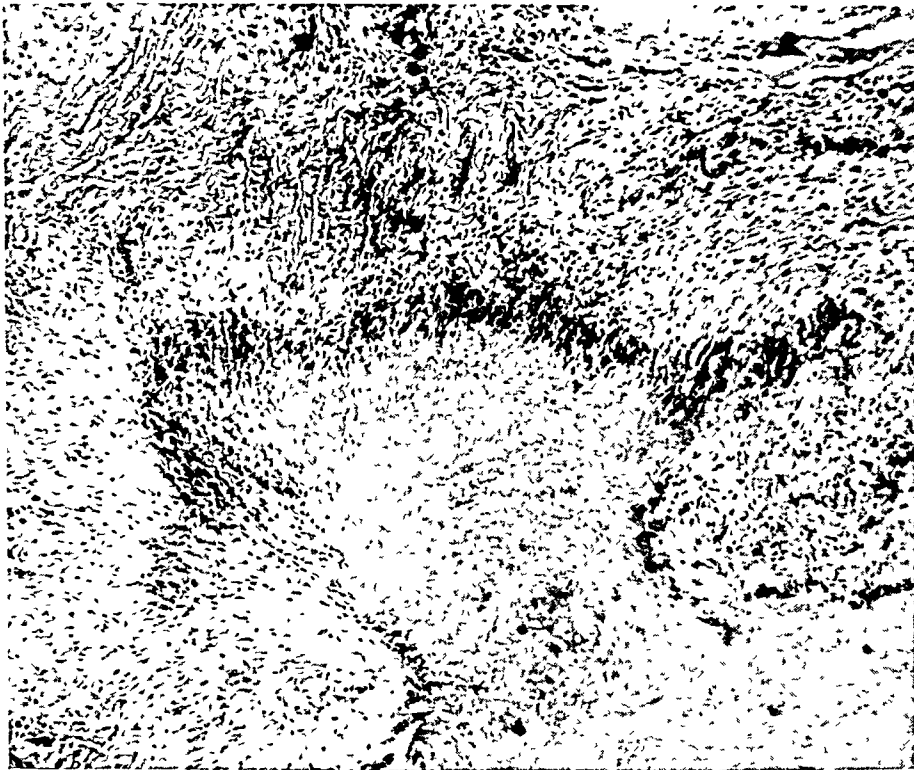
Microscopically it has the same characteristics as those of Dupuytren's contracture, possibly showing a little more perivascular lymphocytic exudate than does that disease, but consisting chiefly of massive desmoid thickening of the fascia which stains irregularly by Masson's method, showing many reddish streaks through the otherwise green-staining collagenous background. These are often noted in connection with tendons or ligaments that are undergoing the preliminary degeneration that leads to calcification.

CHRONIC DESMOSITIS. Orthopedists and physiotherapists are fond of speaking of "chronic desmositis" or "fibrositis," and they mention small, painful lumps that may develop in the fascial attachments of such muscles as the gluteus medius in connection with lumbago. Nevertheless, these lesions are seldom excised, as they tend to regress after treatment, and in the case of autopsies they are not considered to be of sufficient importance to be investigated. Anyone who has suffered from this malady will readily admit the existence of these lumps or nodes. Sometimes the process continues to a point where it is similar to Dupuytren's contracture. Ober has described lesions of this sort in the fascia lata; he believes that they have a bearing upon some forms of sciatica.

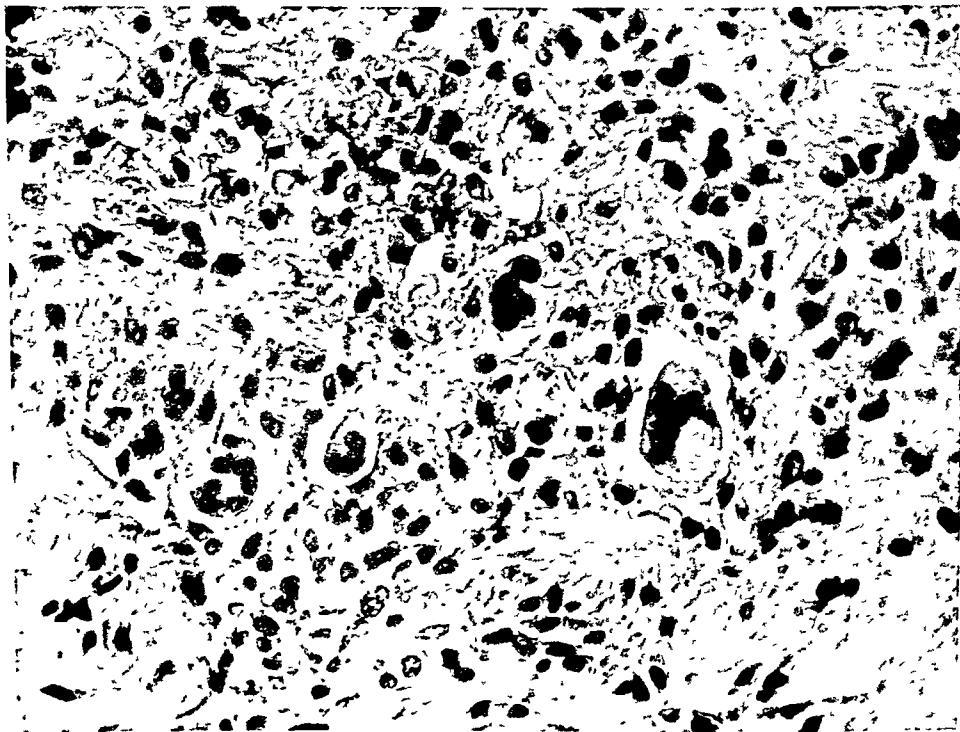
JUXTA-ARTICULAR NODULES. In certain diseases, notably the rheumatoid affections, nodes develop near joints or over tendons and ligaments, and they may be found in the subcutaneous tissue in similar situations. These nodes, which have long been recog-

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Late form of juxta-articular nodule with considerable necrosis and early calcification. Note palisade of macrophages about margin of necrotic focus.



Granulomatous form of juxta-articular nodule showing many giant cells but little necrosis. (Army Medical Museum 64906.)

they may remain at the site of rupture, work their way up or down, and ultimately become firmly attached to neighboring ligaments. This causes pressure on the spinal cord or upon nerve roots. The sinking of the upper upon the lower vertebra will follow the loss of the intervertebral buffer and narrow the bony foramina through which the roots emerge, this is another cause of compression.

Seen in the laboratory, the nucleus pulposus removed from the site of the ruptured disc forms a mass like wet asbestos or cotton waste, it may be 3 to 4 cm. in length, 1 to 2 cm. in width, and about a centimeter in thickness, it is usually more or less shredded by the time it is received. Normally an inert and pulpy mass of fibrous tissue, it undergoes little pathologic change after the disc has ruptured and it has been discharged. Microscopic changes are not very significant, there is the formation of clefts and fissures and some degenerative changes are present. The ligamentum flavum usually becomes fibrosed and is said to be "hypertrophic," although this is probably a misnomer, there is a replacement of elastic by fibrous collagenous tissue and consequent enlargement.

Secondary changes in the joint may be observed, such as the production of osteophytes, which may be subjected to successive small fractures and finally result in hypertrophic arthritis or a picture fairly similar to this. Not only the rims of the joints, but the lateral processes, may come into direct contact and become injured and involved in the hypertrophic bony overgrowth. This condition is being treated by an ever increasing number of surgical excisions of the prolapsed nucleus and segments of the fibrosed ligamentum flavum, so that surgical pathologists should be familiar with the lesions, however slight and trivial they may seem from the pathologic standpoint.

Fractures of Bone The pathology of fractures is really a matter for the surgeon rather than for the pathologist, for they

exhibit nothing very pathologic aside from mechanical trauma and possible deviations from the normal course of bony repair. In the case of ununited fractures, however, it is often necessary to examine the tissue removed at operation to determine how healthy or unhealthy it may be in an attempt to discover why ossification is not taking place as it should. The pathologist may be unable to discover anything more than a fracture line filled with normal connective tissue without any evidence of an attempt at ossification, on the other hand there may be some signs of early ossification, the degree of advancement of which might give some clue as to the prognosis and as to the advisability of continuing or discontinuing treatment. The "pathologic fracture" which results from the weakening of a bone by the presence of a soft tumor metastasis offers the pathologist a golden opportunity, for as this tumor will be present in the tissue removed at biopsy, its type may be readily determined and a prognosis submitted. Evidence of other bony lesions such as osteitis fibrosa, Paget's disease, and the like may be discovered through examination of a biopsy.

Bony Dys trophies **PAGET'S DISEASE** Sometimes erroneously termed "osteitis deformans" this disease usually occurs in later life and may involve one or more bones, or many parts of the skeleton. The bone becomes very much thickened and very light in weight, it looks spongy on section, but the thickening is deceptive, as it proceeds pari passu with a destructive lesion which the osteoblasts attempt to repair. As trabeculae of bone are destroyed, new and more delicate ones are formed into a sort of intraosseous callus, enclosing the fragments of the destroyed trabeculae in their substance and converting the tissue into a thick, light, and spongy mass. Examined by x rays, the bone has a "fuzzy" appearance like frayed yarn. In the case of the skull this thickening may encroach upon the intracranial space and compress the brain. In the long bones thickenings and deformities,

6

Cartilage and Bone

DEVELOPMENTAL ANOMALIES AND VITAMIN DEFICIENCIES

TRAUMA TO CARTILAGE

FRACTURES OF BONE

BONY DYSTROPHIES

GRANULOMATOUS LESIONS OF BONE

INFLAMMATIONS OF CARTILAGE AND BONE

TUMORS OF CARTILAGE AND BONE

CARTILAGINOUS

MUCOID

FROM NOTOCHORD

OSSEOUS

ARTHRITIS

GOUT

These tissues are so closely related and associated that they may best be considered together. There are two types of cartilage: the hyaline variety, which covers articular surfaces, and the fibrous, which is a more or less evenly mixed tissue containing cartilage and collagenous fibrous tissue. The latter is found in tendinous attachments and about the joints of the carpus and tarsus, as well as in the intervertebral discs. As cartilage is formed first in the development of growing bone it is sometimes to be considered as a quasi-temporary tissue; hence many tumors and tumor-like growths show alternate areas of bone or cartilage with mixtures of the two that are often bewildering.

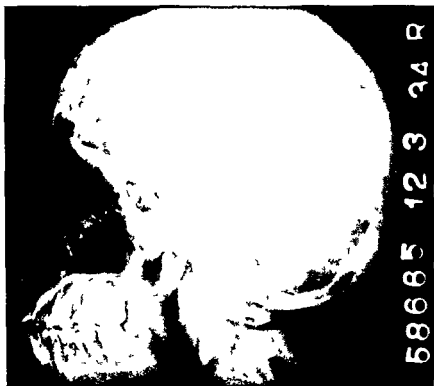
Developmental Anomalies and Vitamin Deficiencies. These do not concern us here excepting in a general way. There may be a deficiency in the development of cartilage or, conversely, overproduction. In rickets, a common deficiency disease, one finds faulty formation of epiphyseal cartilage and a consequent fault in the development of bone from this. Overgrowth of cartilage at the costochondral junctions produces rows of beaded masses lateral to the sternum which are known as the "rachitic rosary." The epiphyseal lesions consist in a faulty deposition of lime salts at the growth centers. Owing to a deficiency of vitamin D in

the diet there is faulty absorption of lime salts, and those that are absorbed are irregularly distributed and deposited in these centers. Should the bone be fractured, exuberant callus is formed, consisting of osteoid, rather than true osseous tissue. Another deficiency disease is due to a lack of vitamin C or ascorbic acid, which may be absolute or relative and produces the hemorrhagic lesions of scurvy or scorbutus. In this there are hemorrhages into the epiphyses with separation of these from the diaphyses, as well as other hemorrhagic lesions into mucous membranes that do not concern us here. Scurvy, however, is a disease that rarely becomes a surgical problem.

Trauma to Cartilage. The commonest trauma is one that had been overlooked for many years until Schmorl and others called attention to it in the late nineteen-twenties. It is known as "prolapsed nucleus pulposus" and results from continued slight trauma to the intervertebral discs in individuals who are burden bearers or who habitually lift heavy weights. There is a progressive flattening and thinning of the discs, and when degeneration supervenes the resulting fibrosis, lack of turgor, and weakening of the annular ligaments bring about protrusion of the disc into the spinal canal. Here the structure becomes ruptured, and its pulpy contents are discharged into the canal where

Albright has described a particular type of this form of dysplasia which occurs in a scattered form throughout the skeleton of young children, particularly girls. It is accompanied by other manifestations such as areas of cutaneous pigmentation and precocious puberty. It exhibits no disturbances

bright's investigation. They find that the disease affects females oftener than males, is more often polyostotic than monostotic, and may affect a large number of bones, 26 of their 90 cases show this markedly polyostotic distribution. When several bones are involved the distribution tends to be uni-



Roentgenograph of skull of patient shown in photograph of Paget's disease. Note "fuzzy" or "woolly" appearance of shadow of the bone and its thickening. Although thick it is also rarefied. (Walter Reed Gen Hosp 2070)

of the blood calcium or phosphorus comparable with those noted in the von Recklinghausen type of adult osteitis fibrosa, although the phosphorus content may be increased. Obviously this represents a different type of lesion which has some similarities to fibrous dysplasia, which will be described next.

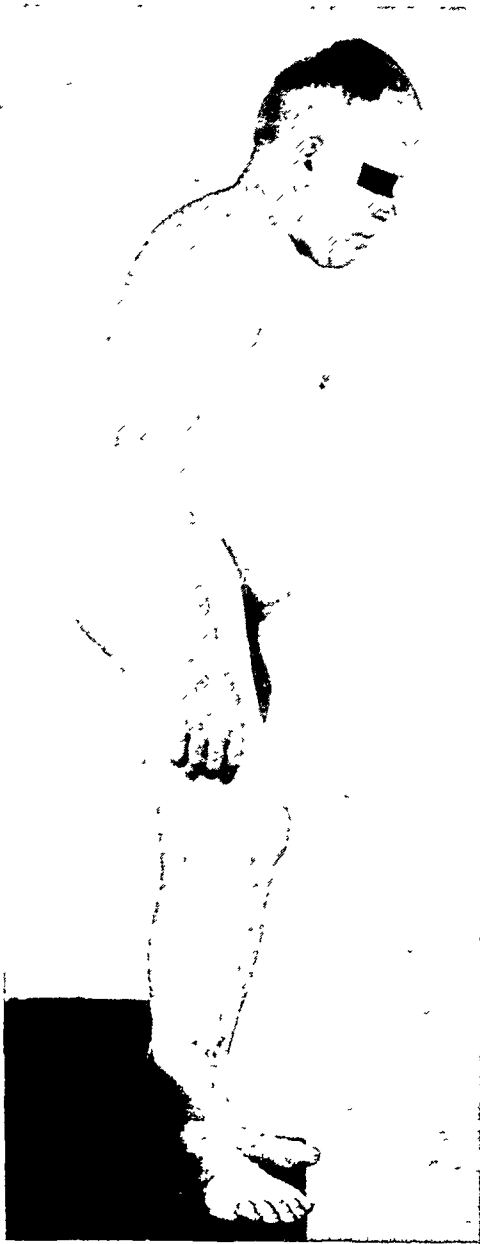
FIBROUS DYSPLASIA Under this name Lichtenstein and Jaffe have described another type of bony dysplasia which they consider to be a congenital disorder that includes Albright's dysplasia. In reaching this conclusion they have reviewed 90 cases, many of which had been included in Al-

lateral. The lesions form large foci of fibrosis that produce either bone cysts or tumor-like enlargements that grossly resemble osteosarcoma, particularly when they occur singly. Grossly, the interior of the bone is filled with a rubbery or slightly gritty gray mass of tissue that may be whittled with a knife and offers little resistance to the bandsaw. There may be areas of dense, scar-like fibrous tissue. Focal areas of degeneration will cause small cyst-like areas filled with a mucinous fluid.

Under the microscope the fibrous tissue is found to vary in its cellularity, some of it being rich in fibroblasts, other parts more

occur which give rise to "saber-shin" legs, marked bowing, and similar distortions.

The microscopic picture is characterized by the presence of a delicate mosaic of fine



Patient with typical Paget's stance. There is anterior bowing of tibiae and moderate enlargement of head, especially the vertex. (Walter Reed Gen. Hosp. 2070.)

lines that represent the outlines of bits of older bone that have been included in the newly formed osseous tissue. There is much delicate callus in the haversian canals and over the surface of the bone, which is always a suggestive sign. The picture is so similar to that of von Recklinghausen's osteitis

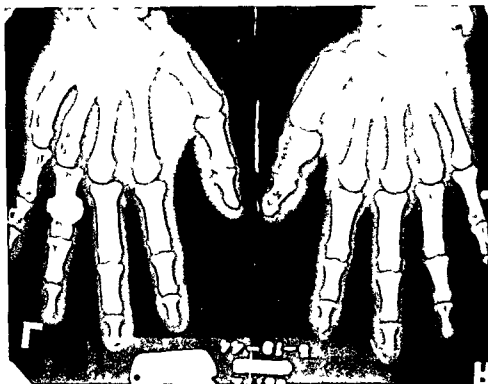
fibrosa that one must be careful not to confuse the two when examining sections. The clinical history will be of service in this connection, for there will be nothing in the clinical pathologic findings to indicate a parathyroid dyscrasia, which would be present in von Recklinghausen's disease. No cause for Paget's disease has thus far been discovered, although it bears a good deal of similarity to bony malformations due to parathyroid hyperfunction.

OSTEITIS FIBROSA CYSTICA. This, too, is a misnomer, as the disease is a dysplasia dependent upon hyperparathyroidism; this fact was unsuspected for a long time and has been established only recently through the work of Albright and others. It affects women oftener than men, is not as common as Paget's disease, and appears at an earlier age. Adenomas of the parathyroid may be demonstrated in the presence of this malady as well as changes in the blood calcium and phosphorus. Deformities and fractures may result from the bony lesion, which usually affects the long bones as well as those of the skull and vertebrae; shorter bones usually escape. Bone "cysts" and "brown tumors" are common, but one should understand that a bone "cyst" is merely a hollowed-out cavity in solid bone that is filled by non-osseous tissue and merely appears to be a cyst when examined under the x-rays. Some of these lesions contain brownish, tumor-like masses that Pick attributes to a reaction to the hemorrhage which often occurs in the cysts and provokes a foreign-body reaction that may reach almost neoplastic proportions.

Microscopic examination reveals a mosaic pattern in the trabeculae that is similar to that of Paget's disease; in addition there is marked fibrous degeneration of the marrow and haversian systems, which become enlarged until the "cysts" are formed. These contain a moderately loose, coarse, fibrous tissue. The brown tumors have the appearance of giant-celled tumors of bone plus a marked degree of hemosiderosis.

calls this "nonsuppurative epiphysitis," but the role of infection and inflammation in these conditions is overshadowed by the degenerative changes, and it is questionable whether one should employ any term ending in "itis" in this connection. The subject has been further befuddled by the fact that a series of eponymic terms have been attached

process accompanying this. The microscope reveals fragmentation and disintegration of the bony nucleus of the epiphysis. A somewhat similar osteochondrosis may develop in the vertebral column in a similar fashion as a result of compression injury from falls from a height onto the feet or buttocks. Clinically the disease is known as Perthes'



Roentgenograph of hands of patient with congenital chondrodysplasia. Note particularly the deformity of right thumb (Army Medical Museum 80799, acc no 111683)

to the same process according to the site of the lesion, one might as well speak of aortic arteriosclerosis as "A's disease" when it occurs in the arch, "B's disease" when it is found in the thoracic segment, and "C's disease" when it affects the abdominal aorta!

This condition is noted in children between 5 and 15 years of age and is found to be situated in the epiphyses of various bones which have not as yet fused with these and are subject to trauma or strain, once the epiphysis has fused with the bone the process ceases. Small areas of aseptic necrosis develop, and there is little evidence to show that there is much of any inflammatory

or Legg's disease when it occurs in the head of the femur, Kohler's in the tarsal scaphoid or patella, Osgood Schlatter's in the tubercle of the tibia, Sever's in the posterior portion of the os calcis, and Kienbock's in the carpal semilunar bone. There is little if any distinction in the pathology of these lesions, and the eponyms should be dropped from the terminology of surgical pathology.

OSTEOCHONDRITIS DESICCANS This condition, often misspelled "dissecans," is a non-infectious, aseptic necrosis that affects the long bones of older individuals and results in the formation of an osteocartilaginous sequestrum that may become detached and

exclusively fibrous. There may be myxomatous areas. Small, newly formed bony trabeculae are distributed throughout the fibrous mass in a rather haphazard fashion; these often have a very immature and poorly organized or calcified appearance. Nests of small, multinucleated giant cells may be observed, but they are not as large or as numerous as those of a giant-celled tumor.

plasias and the tumors; its full appellation is "hereditary deforming chondrodysplasia," and it is most common in young males during youth and adolescence. It takes the form of a retardation of bony growth which produces asymmetry of an often startling type; bones will be too long or too short, bony processes or tuberosities will develop out of all proportion to their normal size, while



Typical area from a costal lesion in polyostotic fibrous dysplasia. Canal-like spaces represent destroyed trabeculae, while marrow has been converted into solid masses of young fibrous tissue. The process is diffuse.

Small masses of hyaline cartilage may also be scattered throughout the fibrous tissue and may undergo calcification without being ossified.

The disease is not commonly encountered in general hospitals; we have noted only one example which was operated upon under the impression that it was a sarcoma of a rib, and this diagnosis was not disproved until microscopic sections were examined. There is a tendency for the lesions to regress spontaneously, and the prognosis is never serious, although bones are naturally weakened by this dyscrasia.

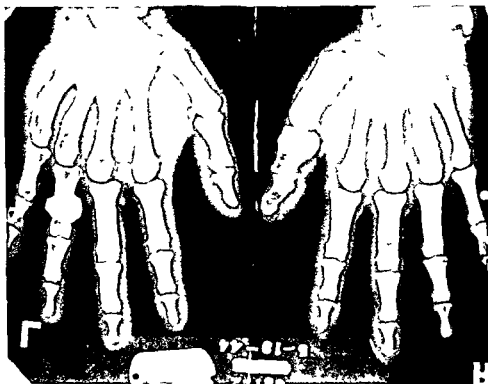
CHONDRODYSPLASIA. Known by a variety of names, this disease occupies an uncertain position somewhere between the dys-

others will be rudimentary and suppressed. Bone cysts are commonly observed. There are also proliferative changes near the epiphyses which cause the early disappearance of the epiphyseal lines in x-ray photographs. Certain portions of the bones may show apparently capricious enlargement, while others will remain normal; many exostoses may appear along the shafts of the long bones. Those bones that are of the "membranous" type of osseous development escape the disease.

OSTEOCHONDROSIS. This term covers a group of juvenile affections of bone and cartilage of obscure etiology, but probably attributable to trauma and interference with the supply of blood to the epiphysis. Boyd

calls this "nonsuppurative epiphysitis," but the role of infection and inflammation in these conditions is overshadowed by the degenerative changes, and it is questionable whether one should employ any term ending in "itis" in this connection. The subject has been further befuddled by the fact that a series of eponymic terms have been attached

process accompanying this. The microscope reveals fragmentation and disintegration of the bony nucleus of the epiphysis. A somewhat similar osteochondrosis may develop in the vertebral column in a similar fashion as a result of compression injury from falls from a height onto the feet or buttocks. Clinically the disease is known as Perthes'



Roentgenograph of hands of patient with congenital chondrodysplasia. Note particularly the deformity of right thumb (Army Medical Museum 80799, acc no 111683)

to the same process according to the site of the lesion, one might as well speak of aortic arteriosclerosis as "A's disease" when it occurs in the arch, "B's disease" when it is found in the thoracic segment, and "C's disease" when it affects the abdominal aorta!

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form a "joint body" or "joint mouse." The fragment may be quite large and covered with cartilage, resembling a detached articular osteophyte. Microscopically the tissue appears to be quite acellular and dried-out (hence "desiccans"), and it reveals the shadows of its former architecture. It may sometimes be invaded by inflammatory cells and foreign-body giant cells may appear.

Granulomatous Lesions of Bone. Infectious granuloma will be taken up in connection with inflammation due to infection; there are other granulomatous lesions of bone, however, that are not a result of infection but rather follow a disturbance in metabolism. In the discussion of lesions of the reticulo-endothelium, "histiocytoses" such as Gaucher's, Niemann-Pick's, Hand-Schüller-Christian's, and others were mentioned; most of these affect bone marrow, but in Hand-Schüller-Christian's disease the compact bone is also invaded and destroyed.

HAND-SCHÜLLER-CHRISTIAN'S DISEASE. This is associated with hypercholesterolemia and occurs in children or young adults. Its manifestations are fairly generalized, as it also affects the lungs and brain as well as the reticulo-endothelial "system." In the bones, particularly those of the skull, it causes foci of rarefaction that are sharply demarcated or punched out, resembling the lesions of multiple myeloma when observed in x-ray films; the defects are circular. The base of the skull is most often affected, the vault is often involved, and lesions may be found in other bones, notably the mastoid air cells and the clavicle, ribs, vertebrae, and long bones. The lesions are firm, yellowish, and putty-like in gross examination; under the microscope one sees large numbers of swollen, vacuolated macrophages in which lipids are readily demonstrable. These fuse to form multinucleated giant cells embedded in granulomatous tissue. Thus, the lesions are not particularly characteristic when observed without a knowledge of the clinical history of the patient.

EOSINOPHIL GRANULOMA. This is a rare lesion first described by Lichtenstein and Jaffe and by Otani and Ehrlich independently of one another in 1940. It is noted mainly in children or young adults. At first it was thought to be monostotic, but later it was proved to be capable of involving several or many bones. The bones of the hands and feet seem to be spared, and the usual distribution is the cranial vault, ribs, vertebrae, and several of the long bones, especially the humerus and femur. There may be slight symptoms, such as pain and low fever, or there may be none. Abdominal pain may usher in an attack. The blood picture may show an eosinophilia of slight degree. The x-ray exhibits rarefaction in areas that are radiolucent and irregular, rather than being cleanly punched out; in the skull, however, sharply defined areas may be seen. The appearance of the lesions is more like that of primary tumors of bone than it is like that of metastases, and it somewhat suggests Ewing's tumor.

The gross lesion shows a more or less hemorrhagic and cystic appearance, with brownish granulation tissue which may be streaked with yellow. There is a good deal of necrosis present. Under the microscope the sections may show areas of granuloma, with very numerous eosinophils and scattered macrophages containing lipids. On the other hand, early lesions may show so many small macrophages so closely packed into an anastomotic tissue complex that the appearance strongly suggests tumor. As the lesion progresses, the lipophages begin to dominate the picture; the eosinophils may continue numerous and conspicuous, or they may not be present in such large numbers. A peculiarity of the dyscrasia is the fact that the lesions may regress spontaneously, healing by fibrosis and leaving fields that somewhat resemble those of the bony dysplasias. Lichtenstein and Jaffe suggest that this condition, as well as Letterer-Siwe's disease ("reticulosis") and Hand-Schüller-Christian's syndrome, constitute different phases in the same process; this may be a

matter of oversimplification, however, as the clinical characteristics of the three dyscrasias are not at all similar, the age incidence is fairly different, and the etiology may also differ quite radically in each case.

Inflammations of Cartilage and Bone

PRIMARY inflammation of cartilage is rare. The forms of bone marrow infection or osteomyelitis are considered in the chapter dealing with diseases of the bone marrow, in connection with this there is usually an osteitis as well in the neighborhood of the inflamed marrow, just as there may be chondritis in that of an acute suppurative arthritis. The bone may also show another form of inflammation that attacks its periosteum, periostitis. This may be primary or secondary to trauma and infection at the time of injury or subsequent to it. The periosteum swells and becomes very painful, and the bone beneath it undergoes necrosis. Such lesions are very common among football, basketball, or hockey players or others whose limbs are apt to receive violent blows in the course of work or sport. We are all familiar with the "stone bruise" of the feet after walking over rocky country in thin shoes or moccasins. Purulent inflammation may result, or the process may remain "aluminous," with a slow course and the formation of a turbid and somewhat viscid fluid beneath the periosteum. In case the lesion should become purulent, the periosteum is raised over a pus pocket between it and the bone which may dissect its way along the shaft.

CHRONIC The osteitis, chondritis, or periostitis may become chronic in the sense more properly termed "subacute." Chronic periostitis usually results in the formation of callus beneath the periosteum and deformity of the underlying bone. As the result of chronic osteitis and osteomyelitis, foci of these may produce circumscribed granulomatous areas which are known as "Brodie's abscesses." With time such an abscess may become a truly cystic cavity filled with clear fluid, such a process is more nearly a cyst than the so called "bone cysts" of fibrous

osteitis, yet it is usually known as an "abscess."

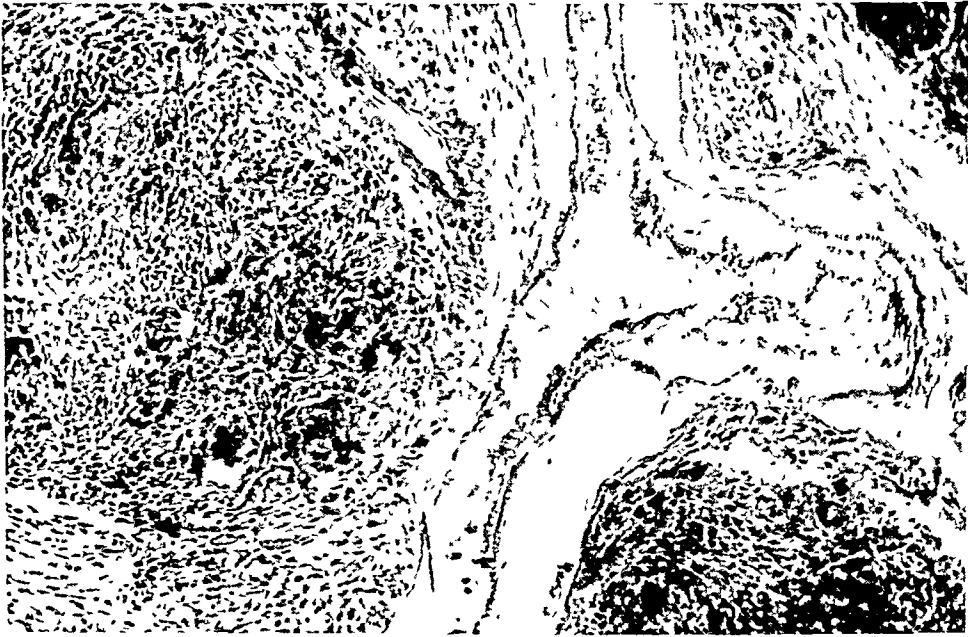
INFECTIOUS GRANULOMA *Tuberculosis* Tuberculous infection of bone is common and accounts for a large group of patients in any hospital, it develops in early life and combines an osteomyelitic with a periostitic and osteitic process. It favors the ends of long bones as its principal site and is very prone to invade the cavities of neighboring joints. Carried to the bone by the blood, the tubercle bacilli initiate lesions in the spongy cancellous tissue where there is the most abundant capillary bed, the disease runs a long course, as there is slow progress accompanied by fibrosis and the formation of new bone that tend somewhat to offset the processes of destruction by repair. The pathology of the lesion is that of tuberculosis anywhere else, but one must be watchful, when examining sections under the microscope, not to confuse osteoclasts and Langhans' cells.

The disease may remain localized at the point where it develops, or it may exhibit a more spreading tendency, involving the marrow and travelling in the shaft to set up new foci elsewhere. Involvement of the shaft, with the production of new bone in an attempt to heal the lesion, may cause thickening and the production of a fusiform dilatation. This is particularly common in the fingers when they are affected with tuberculous osteomyelitis, and it gives them the spindle appearance that is known as "spina ventosa," a term which may puzzle the curious. This means "windy projection" and refers to an imagined similarity to some thing inflated with air. Spindling is due to central absorption of the bone of the shaft and the peripheral layering of new bone over this to compensate for the absorption.

When tuberculosis attacks the spinal column it produces destruction of vertebral bodies with collapse and deformity that leads to various deviations from the normal curves of the spine, of these kyphosis is probably the commonest and leads to "hunchback." Tuberculous abscesses may

develop at the site of such lesions and set up long, burrowing sinuses that may extend over long distances from the original focus before emerging upon the surface of the body. Thus, the psoas abscess may form under that muscle and work down to Poupert's ligament, where it at last reaches the subcutaneous tissue of the groin to produce a "cold abscess."

nasal and facial bones, gives rise to such deformities as "saddle nose" or no nose at all. If the disease develops in the endosteum it forms numerous gelatinous gummata which bring about central erosion and peripheral proliferation; this results in a condition in the fingers similar to "spina ventosa," but now known as "syphilitic dactylitis."



Tuberculous osteomyelitis, showing tubercles in marrow and hazy, granular areas of destroyed bony trabeculae. Typical conglomerate tubercle is seen at left.

Syphilis. The tertiary stage of this disease attacks the shafts rather than the extremities of the bones; the tibia, sternum, and skull and the bones of the nose and face are most commonly involved. In acquired syphilis the infection may attack the outer surface of the bone beneath the periosteum, or it may arise in the endosteum. Being a vascular disease, syphilis interferes with the circulation, and the process is diffuse; there will be an osteophytic overgrowth of the bony surface, or the bone itself may become thickened and eburnated. Sometimes necrosis results, with the formation of sequestra or masses of dead bone similar to those seen in osteomyelitis. Gummata may follow either of these forms of bony inflammation, and there is destruction of the osseous tissue which, in the case of the more delicate

In congenital syphilis the lesions of the newborn do not concern us; those of older children are so similar to those noted in connection with acquired lues that there is little need to dwell upon them. If the tibiae are involved the typical "saber-sheath" deformity is produced, the bones being flattened and bowed anteriorly until they resemble saber sheaths.

TUMORS OF CARTILAGE AND BONE

The tumors that we shall consider here are those of the cartilage and bone proper. Those developing in the marrow are considered in the chapter which deals with the bone marrow; they are not bony tumors and should not be classified as such. The classifications used by the Registry of Bone

Tumors and by Ewing do include these tumors, and for that reason they take a more comprehensive line. The reader is referred to Ewing's "Neoplastic Diseases" for such a classification.

CARTILAGINOUS TUMORS

Chondroma One may observe a variety of cartilaginous tumors that run the gamut from mere overgrowths of cartilage (enchon-

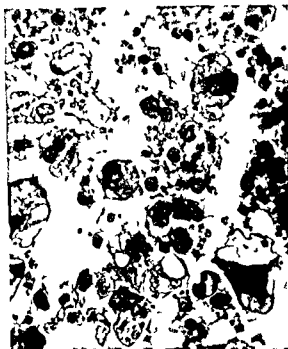


Distorted chondrocytes in chondroma arising from a rib

dromas and enchondromas) to the malignant forms that exhibit little cartilaginous material and consist of renegade cells and mucoid tissue that bear little resemblance to cartilage. A chondroma arises in situations where cartilage is normally found near costal cartilages, near the ends of bones, and in the vicinity of joints or of structures that have cartilaginous rings, like the larynx, trachea, or bronchi. It may also originate from misplaced cartilaginous rests or from teratomas in situations quite unrelated to normal cartilage. For some unexplained reason, cartilage abounds in teratomas and mixed tumors. Small tumor-like masses of cartilage may be found near the ears (the so-called "supernumerary ears") or may arise from the tragus or helix. As a rule, the more important chondromas are to be found in the thorax, where they have their origin from costochondral junctions

Chondroma develops in early life rather than later, it may attain a diameter of 10 to 15 cm or more, it is well encapsulated and, on section, is found to be composed of fairly normal looking cartilage which may show areas of calcification, degeneration, and cyst formation, or ossification. The gross appearance gives little indication of its real make up, which must be determined by microscopic examination. Multiple osteochondromas have been considered under the section on chondrodysplasia, it is doubtful if they are true tumors.

The microscopic appearance of chondroma is that of distorted or of fairly normal cartilage, the "type cells" resemble



High powered field from chondrosarcoma of the radius, showing extreme metaplasia (Army Medical Museum 60673)

chondrocytes, but there may be several of these in a lacuna which should contain but one. They are usually distorted and may exhibit vacuoles in their cytoplasm which Virchow called "Physaliden" from their resemblance to small bladders, "vesicles" would do as well. They generally show glycogen and lipid granules if one looks for

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MUCOID TUMORS

Myxoma The mucoid connective tissue that is normally seen only in the Wharton's jelly of the umbilical cord has an embryologic history that is closely associated with that of cartilage and fat, for this reason it is not unusual to find tumors combining these three forms of connective tissue. This necessitates a rather clumsy nomenclature to indicate the components, as myxolipochondroma and like terms. It seems inadvisable to try to avoid their use, however, as one should indicate the components that have real importance in a tumor. The myxoma usually develops where one would expect one of these elements, as well as in association with nerves where the relationship is less evident. It is a rather firm, well-encapsulated tumor which, on section, is translucent, pale, and very slimy to the touch, with mucoid liquid often dripping from the section surface. It is generally found in the mediastinum, the axilla, and the groin. Myxoma of the cardiac chambers does not concern us.

Microscopically the tumor is composed of stellate cells of great delicacy, best demonstrable in Ramon y Cajal silver impregnations which bring out their multipolar processes very exquisitely. The cells lie in a matrix of gelatinous fluid that is basophil and usually stains blue with hematoxylin. Often enough one will encounter a tumor that combines mucoid with fatty tissue, or mucoid with cartilaginous tissue. This is then called a myxolipoma or a myxochondroma.

Myxosarcoma The malignant form of myxoma is to be recognized with certainty only in microscopic sections. It resembles

the fibrosarcoma very closely, as it has large fusiform cells and a pale matrix, but most of its elements tend to be much more regularly stellate and multipolar than are those of fibrosarcoma. It is definitely malignant and may metastasize. Myxolipoma and myxochondrosarcoma are recognized.

These cartilaginous tumors are all poor material for x-ray therapy and must be extirpated surgically.

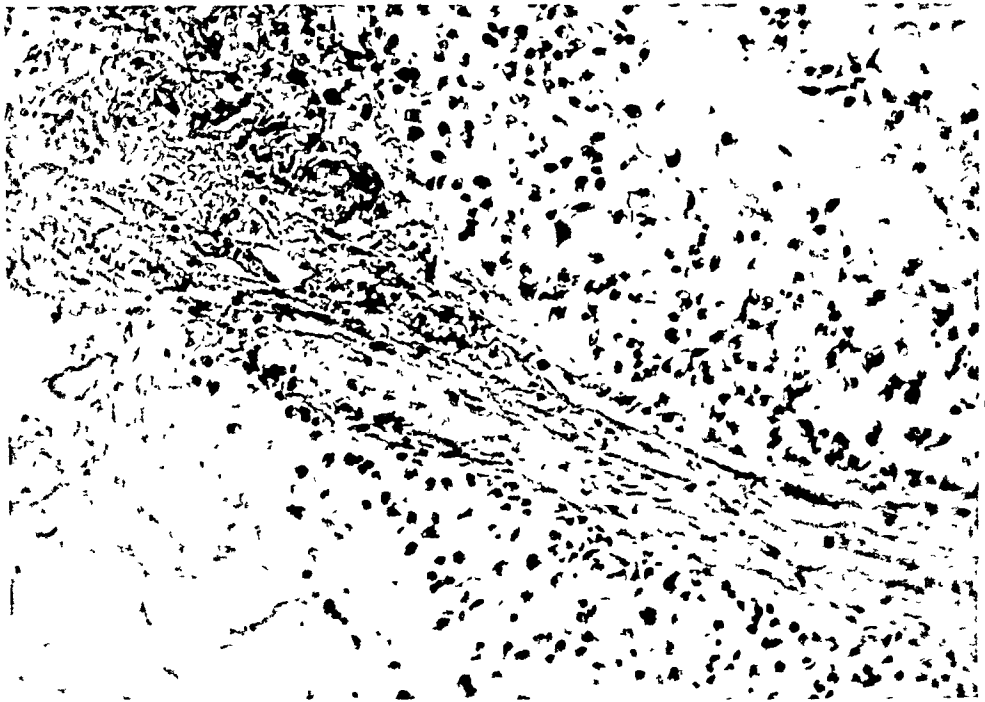
TUMORS FROM NOTOCHORD

Chordoma A tumor developed from rests of the notochord and having many of the characteristics of the myxoma and chondroma, the chordoma is a very rare growth that the pathologist may obtain but once or twice in a lifetime, nevertheless, the time



Sacral chordoma of solid type (Compare this with illustrations of other chordomas). Vacuoles contain either glycogen or lipids or both.

will usually come when he will receive one and have to recognize it. It is usually a tumor of moderate size that is, as a rule, situated near the sacrum or the base of the skull or in the pharynx, although it may arise anywhere along the spinal column. I have seen one in the lumbar region. It originates in rests that have been displaced from the line of the notochord or possibly from such derivatives thereof as the nuclei pulposi of the intervertebral discs. It may



Well-differentiated chondrosarcoma, primary in the rib, shown here in section from spinal dura which it has invaded by metastasis. This well illustrates how little weight should be placed upon degree of differentiation in prognosing cartilaginous tumors.

them. Ranvier recognized four types of structure: tumors composed of a single lobe of hyalin cartilage, tumors formed by a number of such lobes separated by bands of fibrocartilage, a third type showing fetal cartilage, and a fourth cartilage with stellate cells. These distinctions are not very important; that which is important, however, is the recognition of the fact that one can tell little about the future behavior of a chondroma by its microscopic appearance alone. Some very innocent-looking chondromas may metastasize widely, particularly those large tumors that develop from the costochondral tissue and involve the lungs in multiple small growths that look equally innocuous but ultimately kill the patient. It is well to regard the prognosis of these intrathoracic chondromas with a reasonably marked scepticism.

Chondrosarcoma. If this is very malignant it will appear to be very poorly organized, resemble a myxoma to a marked degree, and leave one somewhat doubtful about its true nature until the microscopic sections have been consulted; if it is better



Roentgenograph of very metaplastic chondrosarcoma of lower end of radius. This was attributed to a crushing injury to forearm. (Army Medical Museum 60556.)

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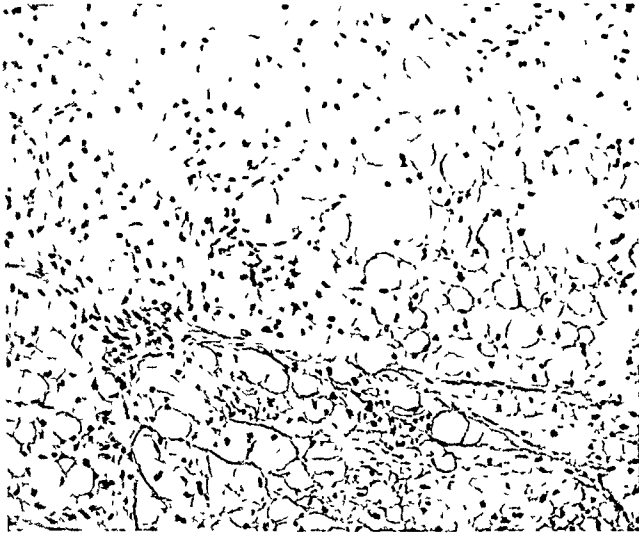
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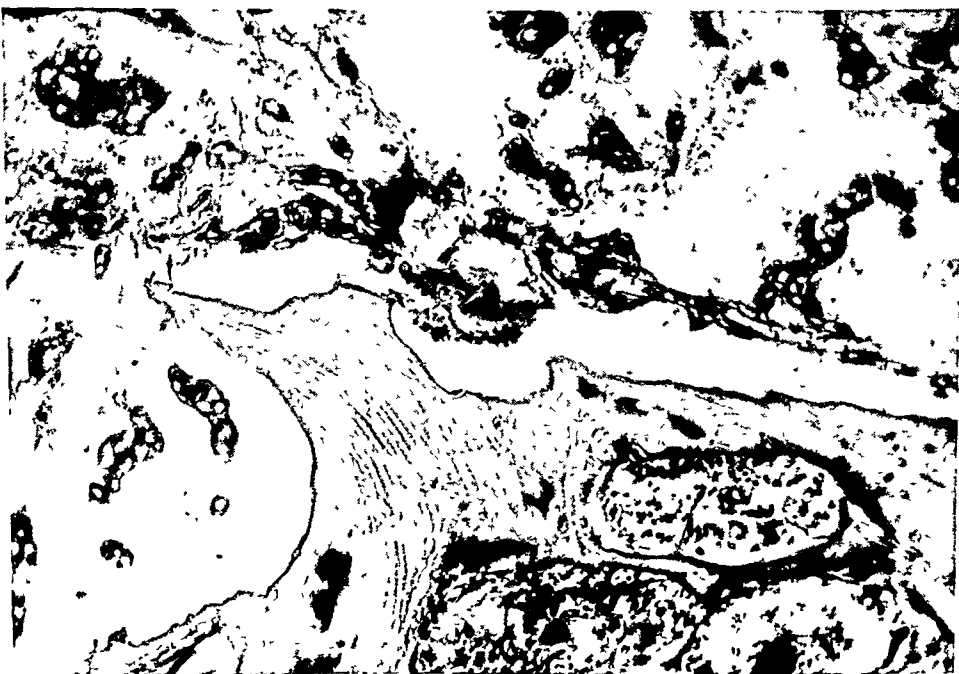


More solid area in chordoma shown in the preceding photograph. Here picture resembles adipose tissue in its microscopic architecture, although tumor is more like cartilage in its gross appearance.

and mucoid, and it rather resembles a mucous carcinoma in its appearance, which is not very distinctive.

Under the microscope it may present a fairly solid mass of large, foamy or vacuolated cells that are packed into alveoli, or

they may form acini that contain mucus and give the tumor almost all the characteristics of a metastatic mucous carcinoma. Thus a mistaken diagnosis is very likely if one does not possess a clear clinical history of the case and some knowledge of the physical findings. Another false diagnosis is myxochondroma, which is imitated fairly closely by a certain form of the chordoma in which there is much mucoid stroma. Special stains will demonstrate glycogen and fat in the cells of the tumor; the Best carmine stain and one of the sudan or Nile-blue methods should always be carried out. The cytoplasm of these cells may also show small, darkly staining spheroids of refractile material, but like the glycogen and lipids, these are also common to these tumors and the chondromas. The site of the tumor and the ruling out of any primary focus that might give off metastases resembling it are the best reinforcements for a diagnosis. A very mucoid and yellowish tumor arising near the sacrum or the base of the skull should always suggest chordoma until proved to be otherwise. A series of x-ray films may have been taken during the development of the tumor in the spinal column, as was actually done in one of our



Chordoma invading body of sphenoid bone. It is composed of irregular groups of vacuolated cells.

cases, here it was possible to observe the progressive growth of a primary tumor's shadow in a lumbar vertebra over a period of three years

OSSEOUS TUMORS

The subject of tumors of the bone is one of the most confused in the literature each author devises his own classification, and the marked differences between any two of these immediately necessitate much correlation and study before the reader can satisfy himself as to what is the approximate truth of the matter. It will be difficult to present the subject here in such a way as to dispel very much of this confusion, but there is a necessity for attempting to do so and thus to render it as clear as possible under the circumstances.

Ewing arranged a "revised classification" for the American College of Surgeons in 1939. This is given below.

	Malignant	Benign
1 OSTEOGENIC SERIES	a Medullary and subperiosteal b Telangiectatic c Sclerosing d Perosteal e Fibrosarcoma medullary, subperiosteal	Exostosis Osteoma
2 CHONDROMA SERIES	a Chondrosarcoma b Myosarcoma	Chondroma
3 GIANT CELL TUMORS	a Benign b Malignant	Epiphyseal giant cell tumor
4 ANGIOMA SERIES	a Angio endothelioma b Diffuse endothelioma	Cavernous angioma Plexiform angioma
5 MYELOMA SERIES	a Plasma cell b Myelocytoma c Erythroblastoma d Lymphocytoma	
6 RETICULUM CELL SARCOMA		
7 LIPOSARCOMA		

It will be noted that the above classification includes tumors discussed in this book under quite other headings, such as blood forming organs, lymphoid tissue, reticular tissue, fatty tissue and the like. In the case of the bone marrow this may be a mistake, to be sure, on account of the intimate association of that tissue with bone, but its functions have nothing to do with bone which

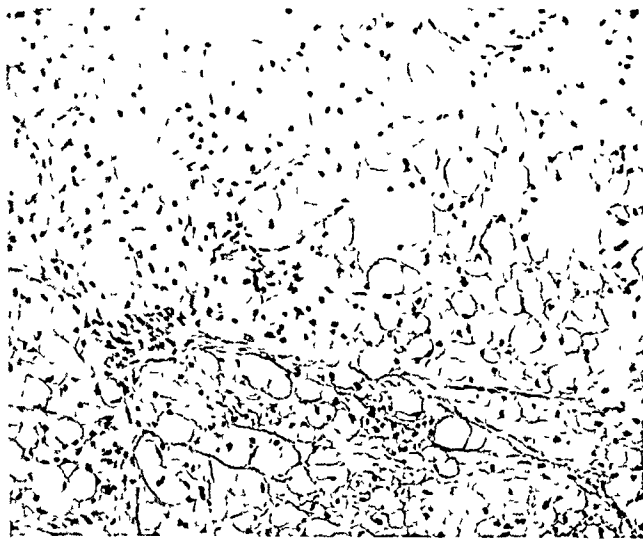
merely serves to house it. If it be damaged by the replacement of its cells by those of metastatic carcinoma (to cite an example) it can be produced in the spleen, lymph nodes, and liver by the process of "myelosis", in brief it can be completely divorced from bone and still function. The classification of Ewing also omits the "osteoid osteoma" of Jaffe, possibly it is intended to be included by implication under "osteoma" as a subgroup. It is also questionable whether the fibrosarcoma of bone is or is not a true osseous tumor, as it forms no real bone.

Geschickter and Copeland give a quite different classification in their excellent book on bony tumors—one based rather more strictly upon the histogenetic features of these growths. But this classification is difficult to apply in teaching the subject and sometimes difficult to align with the current and more prevalent classifications. As that

of the Bone Tumor Registry of the American College of Surgeons is official and standard, it may be well to adhere to it as closely as practicable, omitting the tumors that are not truly osseous and discussing them elsewhere under headings that seem to apply more properly.

Bone develops in two ways: the membranous bones of the skull undergo direct

arise from the under side of a vertebra and extend laterally, breaking out into the soft parts as it increases in size. It is yellow

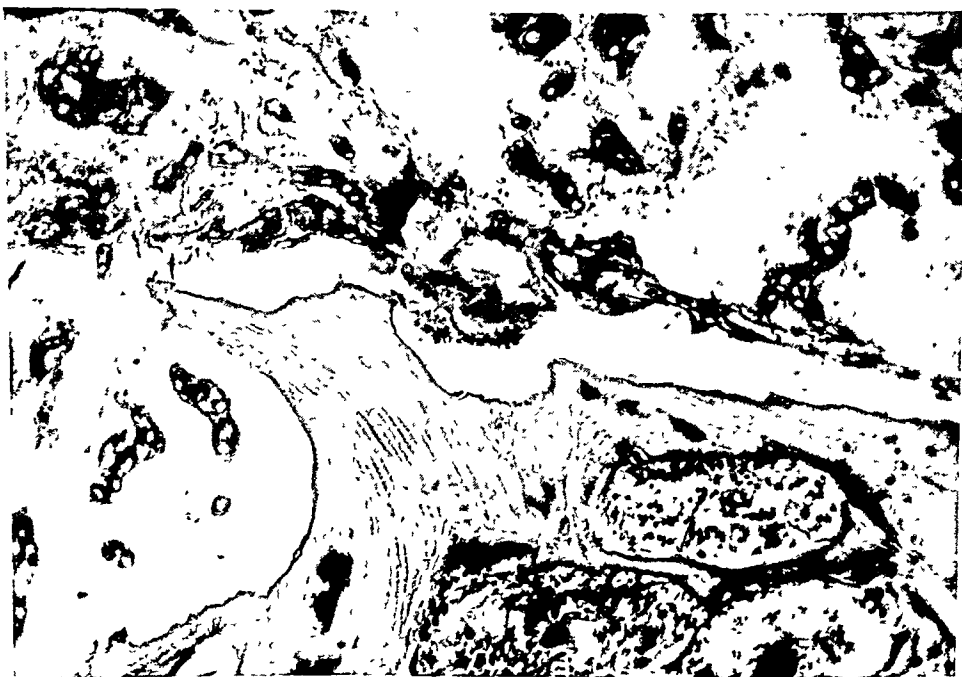


More solid area in chordoma shown in the preceding photograph. Here picture resembles adipose tissue in its microscopic architecture, although tumor is more like cartilage in its gross appearance.

and mucoid, and it rather resembles a mucous carcinoma in its appearance, which is not very distinctive.

Under the microscope it may present a fairly solid mass of large, foamy or vacuolated cells that are packed into alveoli, or

they may form acini that contain mucus and give the tumor almost all the characteristics of a metastatic mucous carcinoma. Thus a mistaken diagnosis is very likely if one does not possess a clear clinical history of the case and some knowledge of the physical findings. Another false diagnosis is myxochondroma, which is imitated fairly closely by a certain form of the chordoma in which there is much mucoid stroma. Special stains will demonstrate glycogen and fat in the cells of the tumor; the Best carmine stain and one of the sudan or Nile-blue methods should always be carried out. The cytoplasm of these cells may also show small, darkly staining spheroids of refractile material, but like the glycogen and lipids, these are also common to these tumors and the chondromas. The site of the tumor and the ruling out of any primary focus that might give off metastases resembling it are the best reinforcements for a diagnosis. A very mucoid and yellowish tumor arising near the sacrum or the base of the skull should always suggest chordoma until proved to be otherwise. A series of x-ray films may have been taken during the development of the tumor in the spinal column, as was actually done in one of our



Chordoma invading body of sphenoid bone. It is composed of irregular groups of vacuolated cells.

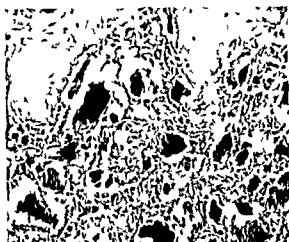
density, both of which are readily demonstrable in x ray films. Microscopically it begins as a local proliferation of osteoblasts which lay down osteoid tissue rather than bone. This is a material that is soft and not calcified and is amorphous, reminding one of hyaline collagenous tissue or masses of amyloid when examined in microscopic sections. It is deposited in serpiginous, connected bands that stain pink with eosin and green in Masson sections. Eventually this may become firmly ossified and converted into true bone. Its much commoner association with malignant tumors of bone makes it imperative that one should recognize the osteoid osteoma for what it is, a nonmalignant tumor which nevertheless produces osteoid material.

Giant celled Tumors. These are essentially osteoclastomas and are beginning to be known by that name. They are considered to be granulomas by some authors, while others believe them to be true neoplasms, at times the dispute over this point has been rather acrimonious. There is much to be said for both views, and the truth may lie somewhere in the middle, they may be granulomas in a sense when they follow trauma and inflammation and true tumors when they arise *de novo*. They are usually nonmalignant and do not metastasize if the primary tumor shows the ordinary characteristics of a giant celled tumor, but they have a malignant variety. This may be derived from the ordinary giant celled tumor, or it may be in reality an offshoot of an osteosarcoma, two types of which show giant celled varieties.

The tumors occur in early life, children and young adults being most frequently afflicted. Their favorite sites are near the epiphyses of the lower end of the femur, the upper end of the tibia, or the maxilla. The vertebrae are occasionally included in this list. Some of the tumors may be extraskeletal so that they may be divided into the skeletal and extraskeletal varieties. On gross examination they may be fleshy and pink or brownish red, those in tendons (see

below) may be bright orange. They tend to be sharply circumscribed in the limbs, less so in the mandible. With time they become whiter and granular and crumbling in consistence.

Their etiology is ingeniously deduced by Geschickter and Copeland, who believe that there are two factors in the long bones the tumors usually arise in or near the cortex after an injury and then work inward into



Field from giant celled tumor of tibia, essentially similar to the illustration of epulis

the epiphysis. These authors believe that interference with the circulation brings about necrosis, necrosis excites an overproduction of osteoclasts to remove the destroyed bone, and following this there is an imbalance that provokes a persistent production of osteoclasts. For the epulis, which will shortly be described, they have another explanation.

Microscopically they are entirely distinctive, being composed of swarms of foreign body giant cells with almost innumerable nuclei (25 to 50 or so) that are like osteoclasts and are embedded in a matrix of plump and actively growing fibroblasts and histiocytes. Silver impregnation reveals an ubiquitous network of reticulum that envelopes all the cells but appears to be broken up by the giant cells which often lie in spaces cleared in the otherwise dense reticulum. These cells are then found to con-

ossification of fibrous tissue, much like that noted in extraskeletal ossification; other bones must pass through the cartilaginous stage, the cartilage being laid down in fibrous tissue and later canalized and rearranged by osteoblasts and osteoclasts. This is not the whole story, for bone continues to undergo absorption and rearrangement throughout the growing period of a child. Certain bones possess epiphyseal centers of bony development, others have scattered centers from which bone develops and fuses with that produced by neighboring centers. All this tends to make osseous development complicated and the recourse to a strictly histogenetic classification of bony tumors difficult. Add to this the phenomena of callus formation in the repair of fractures and one has another complication which is often a part of the mechanism of growth in osseous neoplasms. Therefore, if bone in its normal development and repair is a complicated and labile tissue, its tumors will exhibit the same lability and vary greatly from one another in their appearance and characteristics. Some of them recapitulate cartilaginous development, others membranous; others resemble perverted callus. Some of them grow very rapidly, others are more leisurely.

Before they are described in detail it would be well to say that they usually afford very tricky material for biopsies and for diagnosis by means of these. The aspiration biopsy will seldom succeed in the osseous tumors because if they are not solid and bony they are too fibrous to be aspirated easily. It is questionable whether the trauma incidental to operative removal of enough bone for a biopsy is not in itself dangerous. It is true that bits of tumor that have invaded the soft parts are sometimes readily procured, but these frequently resemble fibrous tumors so closely that the pathologist is misled.

Nonmalignant Tumors of Bone

Osteoma. Like the fibroma, the osteoma is a border-line growth and is roughly

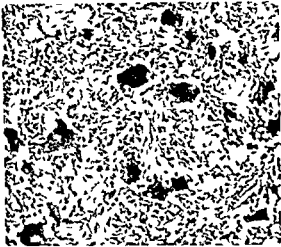
analogous to a keloid in many instances, as it may represent a reaction to injury or inflammation. It may also arise spontaneously and resemble a fibroma in that respect. When such tumors are definitely traceable to injury or irritation they are known as "exostoses," growths that are usually covered and combined with a good deal of cartilage and hence sufficiently mixed in nature to be called "osteochondroma." Osteophytes that form as small spurs in connection with fractures or with such diseases as hypertrophic arthritis or syphilis are not to be included here, as they are not tumor-like. An outgrowth into the cavity of the shaft from the endosteum is known as an "enostosis," but it differs little, if at all, from an exostosis. Large osteomas may be found anywhere in connection with the skeleton as independent, autonomous tumors with or without cartilaginous admixture; these are the true osteomas or osteochondromas. Like normal bone, they may present two types of structure: solid or eburnated and spongy or cancellous. They may be hereditary and familial and occur as multiple nodules at the ends of long bones, or they may be single and sporadic. They occur in youth between the ages of 10 to 25 years, usually giving a mixed picture of bone and cartilage in x-ray films. The base is bony, the surface of the tumor less dense and more translucent. They should be carefully removed, not taken off piecemeal with a curette or chisel.

Microscopically they so closely resemble normal bone and cartilage that it is often difficult to determine from a given section whether one is examining part of the tumor or a portion of the bone in which it grew. Its architecture may be somewhat haphazard, but it is usually comparatively orderly.

Osteoid Osteoma. Jaffe recently described a nonmalignant tumor of adolescents and young adults that usually involves the tibia and femur; macroscopically it is a small growth that shows areas of rarefaction surrounded by a zone of increased

balance is set up similar to that in the case of cortical giant celled tumors of long bones, and the giant cells continue to proliferate and form a tumor. This is essentially the same in most particulars as that of the long bones.

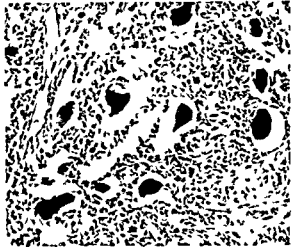
"Xanthosarcoma of Tendons" This tumor merits the prefix "xantho" as it is definitely yellow or orange in most instances, but it is not a sarcoma. It represents a giant celled



Section from an "epulis" or giant celled tumor of alveolar processes of jaws. Giant cells with innumerable nuclei lie in a fibrous matrix which is relatively acellular.

tumor that is almost indistinguishable from the rest of the group. Here, again, Geschickter and Copeland come forward with a most ingenious explanation of the reason for tumor apparently indigenous to bone appearing in tendons. They note that the giant celled tumors of the patella (which is a sesamoid bone) are very similar to those of tendon, hence they believe that they are derived from sesamoid bones. They state that these growths are very prevalent upon the flexor side of tendons of the fingers, we have had a large number from the extensor surface that lay just beneath the skin. The giant celled tumor of tendon, as it is better called, differs from the typical giant celled tumor of bone in possessing large numbers of foamy cells usually called "xanthoma cells." They are histiocytes filled with lipid

droplets. Ewing mentions them as being found in giant celled tumors of bone. Very often the matrix of such tumors may con-



Giant celled tumor of tendon sheath showing foreign body giant cells embedded in dense collagenous tissue and masses of small, polyhedral cells.

sist of rather metaplastic, actively growing fibroblasts which may show mitotic figures, but in spite of this they appear to be uni-



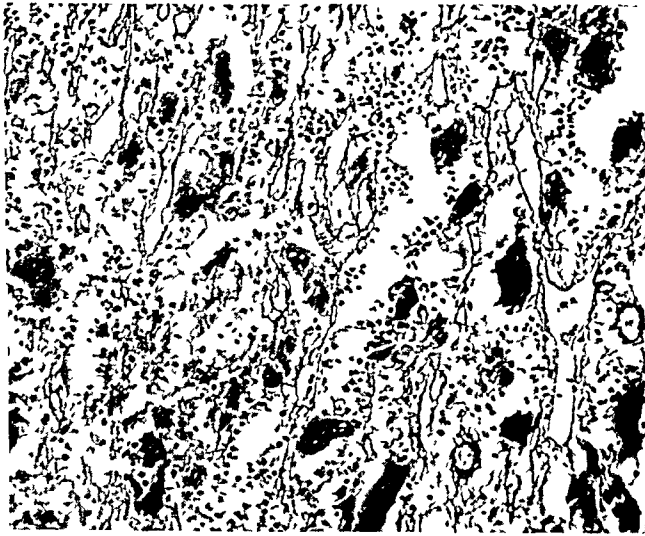
Xanthomatous area in giant celled tumor of tendon sheath. These are vesicular cells that lend to the tumor its yellow color on gross examination.

formly nonmalignant. Once resected, they seem to be cured, and they do not recur.

MALIGNANT GIANT CELLED TUMOR There is some dispute about the existence of such a growth, in the sense that it originates in

tain clumps of argyrophil material which may represent the broken-up network. Mitoses and metaplasia are not observed in the nonmalignant variety.

That these growths are closely related to those derived from reticulo-endothelial tissue is almost obvious if one studies them in silver impregnations; Ewing pointed out this relationship to endothelium in his lec-



Silver impregnation demonstrates reticular matrix in giant-celled tumor of tibia. This leads one to assume that it is a reticulo-endothelioma. (Compare with illustration of gouty tophus in Chapter 2.)

ture course to students, which was published as a small volume, but avoided discussing the idea in his large textbook on tumors. For some reason this concept has never been received with any enthusiasm, seemingly arousing a good deal of antagonism.

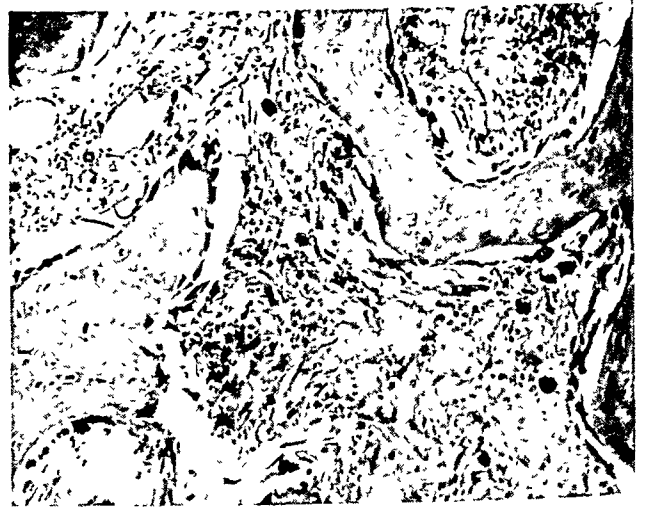
Giant-cell tumors may be divided into two types: skeletal (including the epiphyseal, brown, and spindle-celled tumors) and extraskeletal (including epulis and "xanthosarcoma of tendons").

SKELETAL TYPES. *Epiphyseal Giant-celled Tumor.* This needs no further description, as it is the type upon which the foregoing paragraphs of general consideration were based.

"Brown Tumor." This is usually found in bone cysts in connection with osteitis fibrosa cystica; according to Pick it is a

granuloma which responds to the hemorrhages into the cysts produced by this disease. The tumor's brown color is due to deposited hemosiderin from the hemoglobin of the extravasated blood. Otherwise it is much the same as the preceding type.

Spindle-celled, Giant-celled Tumor. Geschickter and Copeland differentiate this as a more slowly growing and fibrous form that abounds in fusiform fibroblasts and develops more centrally than the typical giant-celled tumor. As there is less interference with the blood supply, these tumors produce fewer osteoclasts and are pale. This may also be accounted for on the basis of their more central location, where fibroblasts are more likely to be abundant than are osteoclasts.

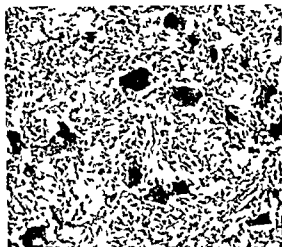


Field from a "bone cyst." Chief lesion consists of fibrosis of marrow and closely resembles that of chronic osteomyelitis. Bony trabeculae are in relatively good condition here, but many have been destroyed outside of this field.

EXTRASKELETAL TYPES. *Epulis.* This form of giant-celled tumor is found in early life about the gingival margin and that of the alveolar process in the neighborhood of the bicusps or anterior teeth, not in the proximity of the molars. As the former are deciduous teeth and the latter permanent, Geschickter and Copeland deduce that the odontoclasts which loosen the "milk teeth" prior to their replacement by permanent teeth form the nidus of the tumor. An im-

balance is set up similar to that in the case of cortical giant celled tumors of long bones, and the giant cells continue to proliferate and form a tumor. This is essentially the same in most particulars as that of the long bones.

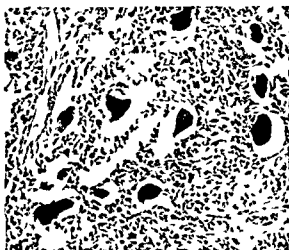
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Section from an "epulis" or giant celled tumor of alveolar processes of jaws. Giant cells with innumerable nuclei lie in a fibrous matrix which is relatively acellular.

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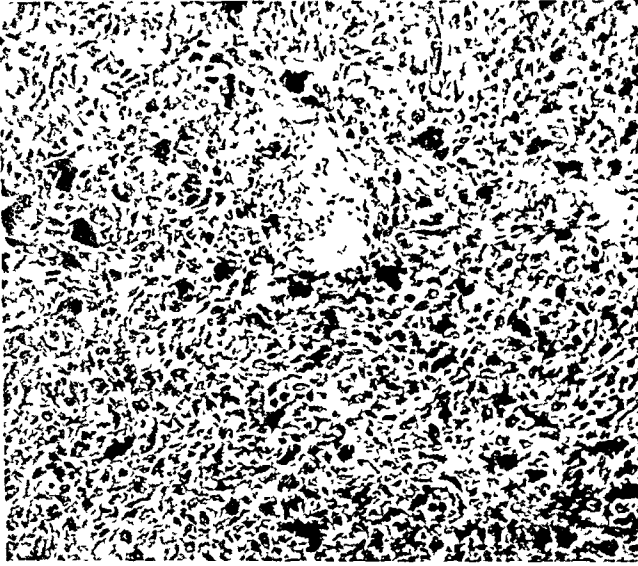


Xanthomatous area in giant celled tumor of tendon sheath. These are vesicular cells that lend to the tumor its yellow color on gross examination.

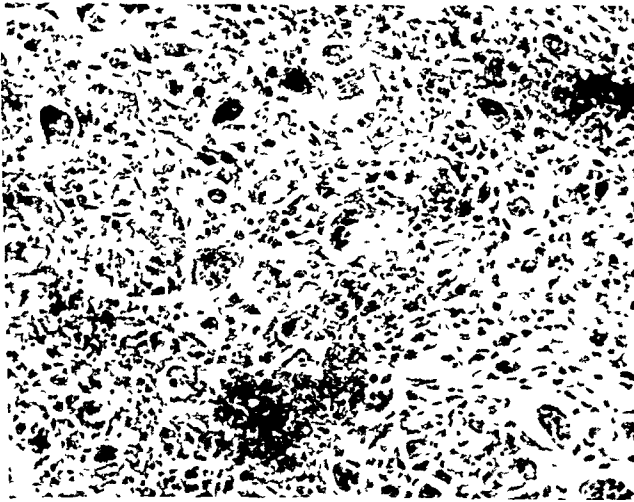
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MALIGNANT GIANT CELLED TUMOR There is some dispute about the existence of such a growth, in the sense that it originates in

a nonmalignant giant-celled tumor. If one takes the view that the latter is reticulo-



Malignant giant-celled tumor of bone. Few of the giant cells are of foreign-body type, most of them being neoplastic. Note also that smaller cells of the tumor are plump and primitive, not well differentiated.



Malignant form of giant-celled tumor known as "extraskeletal" and apparently unconnected with bone. This one arose in muscles of thigh and killed the patient in a year's time by metastasizing widely. Note that smaller cells are primitive, although giant cells do not differ from those of any giant-celled tumor.

endothelial in nature, there will be no difficulty in correlating the malignant giant-celled tumors that are found with that growth. Instead of many of the malignant giant-celled forms that metastasize being

"mistakenly diagnosed," the telangiectatic osteosarcoma may be "mistakenly classified." It could represent a malignant form of giant-celled tumor in some of its varieties although its sites of incidence are somewhat against this assumption. The matter is one that may well be investigated further. The microscopic appearance of the malignant variety of giant-celled tumor is very much like that of the osteolytic or telangiectatic osteosarcoma, excepting that there are more regular osteoclasts, more compact growth and less vascularity than these usually show.

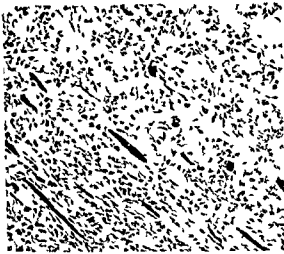
Malignant Tumors of Bone

Osteogenic Sarcoma. Before taking up the various forms of this neoplasm it will be well to make a few general remarks on the subject. Boyd states that it has been estimated that one out of every three sarcomas is an osteosarcoma; thus it is not uncommon. It usually occurs before the age of 50 and prefers the bones of the lower limbs, the ends of long bones and the knees being the favorite sites; the femur, tibia, humerus, pelvis, and fibula are affected in that order. At one time the tumors were common among radium dial painters who pointed their brushes by moistening them with their lips, thus absorbing radioactive material from the "paint." This caused osteitis that produced osteosarcoma and killed 27 per cent of the patients.

Malignant tumors of bone are mostly characterized by pain which may be agonizing and which may precede the development of more obvious symptoms. Trauma is often cited as an etiologic factor, but Ewing has pointed out that the pain and clumsiness incident to the presence of a hitherto unnoticed tumor may provoke the trauma by causing the patient to slip and fall, rather than the reverse (stimulation of growth of a tumor through the fall and its consequent trauma). These new growths metastasize widely, but they do not involve other bones, as they prefer such organs as the lung for their spread.

The Bone Registry classification divides osteosarcomas into five categories Medullary and Subperiosteal, Telangiectatic, Sclerosing, Periosteal, and Fibrosarcoma

MEDULLARY AND SUBPERIOSTEAL TYPE
This group of tumors is the "chondromyxosarcoma" of Geschickter and Copeland, it apparently includes as well their chondrosarcomatous form of osteolytic sarcoma in its "medullary" subdivision Most of these



Osteogenic sarcoma invading skeletal muscle Black streaks are surviving muscular fibers

arise beneath the periosteum, growing into the medulla and spreading upward and downward along the shaft, which is thus destroyed After this, the tumor breaks into the surrounding soft parts and muscular attachments It is found in children and young adults from 14 to 24 years of age The knees, shoulders, and pelvic girdle are affected most frequently and in that order The ends of the diaphyses of long bones (lower end of femur and upper end of tibia) are involved X ray films show erosion and destruction of bone with the periosteum raised into a cuff like structure beneath which appears a triangular space known as "Codman's reactive triangle" which is very distinctive There may be condensation of the medulla instead of decreased density, radiating lines pass out into the shaft

Grossly the tumor is a large fusiform swelling in the situations noted, on sawn

section one notes the destroyed shaft entering or traversing the core of the tumor that is of a very heterogeneous appearance mottled and composed of alternating areas of cartilage, bone, and fibrous tissue There is usually more or less hemorrhage in scattered foci Under the microscope such tumors are found to present variable pictures which may recapitulate cartilaginous osteogenesis, may resemble fibrosarcoma and will probably exhibit areas of surviving or regenerating osseous tissue from the affected shaft Foreign body giant cells may be present or absent, and one often notes neoplastic giant cells of the type noted in sarcomas of connective tissue in general and not at all similar to foreign body syncytia Some of these osteosarcomas may present a preponderance of such neoplastic giant cells and qualify as one of the types of "true giant celled sarcoma"

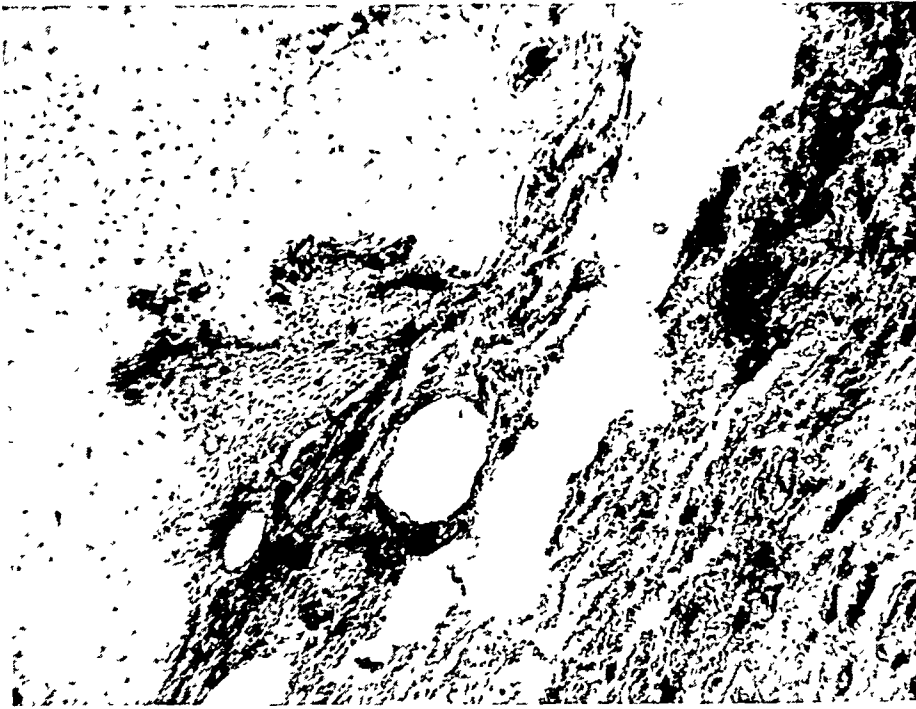
TELANGIECTATIC OSTEOSARCOMA (Central Osteosarcoma, Osteolytic [Osteogenic] Sarcoma, "Malignant Aneurysm of Bone")

This is a tumor of children and young adults that appears around the age of puberty (10 to 20 years) and adolescence, occurs in the ends of long bones (lower end of femur and upper end of tibia), and may be found less frequently in other bones It is described elsewhere in this book under blood forming organs, but it will do no harm to emphasize here its characteristics as compared with those of the bony tumors treated in this chapter Geschickter and Copeland describe a cartilaginous form of this growth that has almost the same age incidence and distribution, which is probably included in Ewing's "medullary osteogenic" type

Telangiectatic osteosarcoma is a much discussed neoplasm which often resembles a reticulum celled sarcoma and shows a great deal of well developed reticulum which, being seldom looked for by the average pathologist, is often missed Some of these neoplasms have been thought to arise in the marrow cavity of the bone from vessels, as the tumor is very rich in these, so

much so that it often emits a bruit on auscultation (hence "malignant aneurysm"). It grows with astonishing speed and spreads up and down the shaft, eventually emerging into the soft parts, weakening the bone, and causing pathologic fracture. Its gross appearance is that of an hyperemic and mottled growth that occupies the center of the shaft and may or may not exhibit ero-

is, of course, a regular feature in this very vascular growth and may be very extensive. Mitotic figures abound. The prognosis is very grave indeed; early amputation is the only expedient, and metastasis occurs so early that the tumor may have spread before operative measures are taken. It runs a fatal course that may be reckoned in months. In Ewing's (Bone Registry) classi-



Osteogenic osteosarcoma metastasizing to lung, some of which appears in lower right of field. This particular tumor is producing much cartilaginous material.

sions and areas of break-through, according to its degree of progress. At first these tumors may seem small and insignificant, lulling the surgeon into a false sense of security and causing him to content himself with a mere curettage of the bone. The x-ray reveals the central destruction or, in the early stages, a single area of rarefaction.

The microscopic appearance of this growth is tied up with the vascular and adventitial endothelium, some examples are much like reticulum-celled sarcoma, others resemble true giant-cell sarcoma like that which may complicate the preceding Type A. The cells vary from fairly well-differentiated fusiform or ovoid types to very grotesque gigantic examples which may or may not be multinucleated. Hemorrhage

and areas of break-through, according to its degree of progress. At first these tumors may seem small and insignificant, lulling the surgeon into a false sense of security and causing him to content himself with a mere curettage of the bone. The x-ray reveals the central destruction or, in the early stages, a single area of rarefaction.

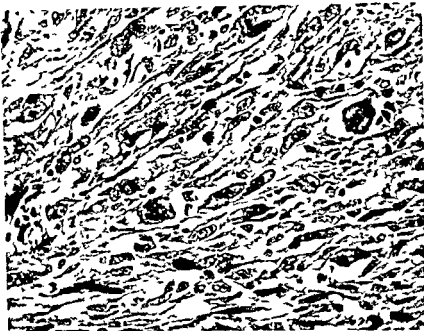
fication the reticulum-celled sarcoma may represent the extreme of the scale of histologic pictures noted in osteolytic or telangiectatic osteosarcoma, at the other end of which are the more compact and fibrous examples.

SCLEROSING OSTEOSARCOMA (Osteoblastic [Osteogenic] Sarcoma). This type involves the ends of long bones and forms large, slow-growing tumors of great density in the lower end of the femur or upper end of the tibia, less often in other situations. It is very solid and eburnated and tends to extend up or down the medullary cavity in the form of a club-shaped mass that may involve as much as half of the shaft, sometimes breaking into the epiphysis. It does not tend to invade the soft parts, although it may cause

a sort of ossifying myositis in the muscular attachments. It is characterized by aching pain, and its incidence is in the range between 15 and 35 years of age. X-ray films show a large fusiform enlargement that does not lift off the periosteum and produce a reactive triangle and is characterized by radiating spicules of dense bone that are delicate and likened to sun rays. "Sun ray shadows" are typical of this tumor.

leisurely manner and have killed patients some time after amputation was thought to have cured them. Unfortunately, amputation is the only recourse in the case of most of the osteosarcomas.

PERIOSTEAL SARCOMA This group develops from the outer layers of the periosteum and tends to grow outward without changing the condition of the bony shaft. It affects children and young adults (14 to 21 years)



High powered photomicrograph of periosteal sarcoma from upper end of humerus in elderly male (Army Medical Museum 66193)

Grossly it is solid and bony looking, with the shaft embedded at the center and exhibiting considerable destruction. The microscope shows an abundant matrix of eburnated bone or many delicate and poorly formed spicules that are solid and refractile, looking very inert and almost crystalline at times. The matrix encloses small areas of atypical spindle cells with hyperchromatic nuclei. Mitotic figures are not abundant, and the tumor has a much less malignant appearance than do the others of the osteosarcoma family. Ewing points out that the rich capillary supply of these sclerosing tumors lends to them potential malignancy, inasmuch as their cells readily enter the circulation. Metastases grow in an equally

and attacks the ends of long bones near the knee and shoulder, also affecting the pelvic girdle at times. It may arise near the attachment of muscles to bone. The x-ray appearance is that of an envelope which is not very opaque and encloses an intact shaft. As it produces no bone, the shadows that may radiate from it are caused by osteoid tissue, which this tumor may manufacture in small quantities.

Grossly the periosteal sarcoma is fusiform and tends to envelop rather than to invade the underlying shaft. So completely may it enclose this that it may also spread to contiguous bones. It is a firm, cellular, and vascular growth that does not tend to break down nor to be the site of hemorrhage. Its

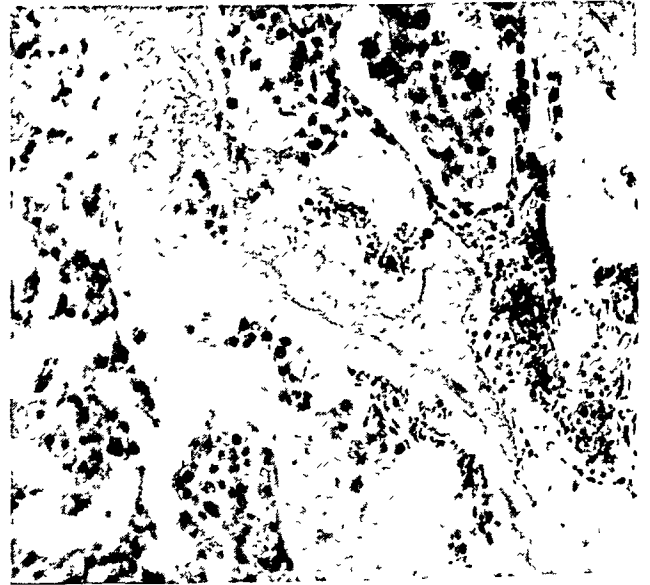
growth is rapid and malignant. Microscopically there is a good deal of resemblance to a fibrosarcoma of dense architecture comprising small, fusiform cells; these may lay down a good deal of hyalin matrix which may undergo calcification without, however, becoming ossified; osteoid tissue is the nearest approach to bone formation and very little of this may be produced. Metastases occur early and are widely disseminated throughout the body, so that here again early amputation is indicated.

Fibrosarcoma (Medullary and Periosteal) (Extraperiosteal Sarcoma). This has a much later incidence, being found after the thirtieth year. It affects the lower extremities, occurring at the lower end of the femur and upper end of the tibia but lying at a point where the shaft joins the lower or upper heads of these bones. Its rate of growth is slow. It may originate inside or on the outside of the bone, destroying the shaft and lifting off the periosteum as it grows. It is firm and fibrous and may be cartilaginous. X-rays show the medullary type to be a sharply demarcated, more or less solid and opaque shadow, together with signs of an eroded and destroyed shaft; the periosteal type is dense and spares the shaft, while the shadow spreads into the soft parts.

Microscopically it is characterized by an excess of hyalin fibrous matrix over cellular components. Large fusiform cells lie in this matrix, which is decidedly avascular. Osteoid tissue and areas of calcification may be noted. Ewing considers this tumor to be mildly malignant and advises radiation by implication, as he states that many examples regress after this treatment. Geschickter and Copeland are in marked disagreement with this and give a poor prognosis; they advise amputation.

Other Malignant Tumors of Bone. Disregarding the rare liposarcomas which may develop in the bone marrow, we may proceed to those tumors which produce the majority of malignant lesions in bone as distinguished from those of bone: these are mostly carcinomas of a wide variety of

origins. The malignant myeloid tumors are discussed under the blood-forming organs. The breast, prostate, kidney, lung, uterus, and many other organs may contribute to



Bony metastasis of mammary carcinoma of solid canalicular type.

the long list of metastatic carcinomas involving bone. Some of these may emit a few metastases, like the clear-celled carcinoma of the kidney (hypernephroma); others may



Metastasis of a "hypernephroma" to bone. Large black structure at upper right and paler one to its left are surviving bony trabeculae which have not as yet been destroyed.

pepper the skeleton with metastatic foci, particularly the prostate, which has access to the vertebral column through the pre-vertebral plexus of veins described by Bat-

son The laboratory of a general hospital will receive vastly more specimens of metastatic than of primary bony tumors, which are usually concentrated in institutions for diseases of bones and joints or for "cancer" in such large cities as New York. The pathologist of the small town hospital will probably stand a much better chance of obtaining and studying osseous tumors than will the man situated in one of the metropolitan general hospitals.

the immediately adjacent bone that underlies it. There are two principal types of arthritis: adhesive or proliferative, and degenerative (of Nichols and Richardson). These usually go under the names of "rheumatoid" and "osteo" arthritis.

Rheumatoid Arthritis This is the usual "chronic rheumatism" that begins in synovial membranes of one or more joints at the margins of the cartilage and may stop there. A growth of granulation tissue ex-

TABULAR SYNOPSIS OF OSSEOUS AND ALLIED TUMORS

(Condensed from Geschickter and Copeland)

Tumor	Age	Location	Appearance under X ray	Treatment
Osteochondroma	10-25	Elg ¹	Oseous base and cart cap	Surg removal
Chondroma	20-30	Hnds, ft, ribs, manub sterni	Translucent areas, "fuzzv" or cystic	Leave alone if symptomless
Periosteal Osteosarcoma	14-21	Elg ¹ , ² pelv, knee, shoulder	Envelope encl shaft No bony shadows	Amputation
Secondary Chondrosarcoma	35-55 Males 2 1	Same as osteochondroma	Central osseous destruction, shows periosteal reaction	Amputation
Sclerosing Osteosarcoma	15-35	Elg ¹ , lower extr	Sun ray picture	Radical amputation
Osteolytic Osteosarcoma	10-20	Elg ¹ at knee	Central destruction	Amputation
Osteolytic O S Cartil type (Ewing's medullary ³)	14-19	Elg ¹ knee shoulder	Somewhat cystic, may be single rarefied area like Ewing's tumor	Amputation
Giant cell Tumor	Adults	L E ² femur, U E ³ tibia	Absorpt, enlgmnt near and incl epiphysis, subcort ext centrally	Curettage
Ewing's Lymphoblastoma	5-25 Males 2 1	Shaft long bones	Diffuse defect at midshaft with shadow, cortex thick and smooth	Amp, resect & irradiat
Myeloma (plasma cell)	40-70	Ribs, spin col, vault skull Arms and legs usually spared	Punched out defects like Swiss cheese	No avail
Fibrosarcoma	30 upward	L E ² femur U E ³ tib sparing heads of bone	Destruction from without inward	Amputation

¹ Elg = ends of long bones

² L E = lower end

³ U E = upper end

ARTHRITIS

We have already briefly discussed the inflammatory lesions of the synovial membranes in the section on serous membranes, but in joints there are added elements in the articular surfaces such as cartilage and

tends like a pannus over the articular surface, as the process continues the cartilage becomes denuded through destruction of the synovial membrane, and it may be destroyed entirely, leaving the subarticular bone in turn denuded and covered only by

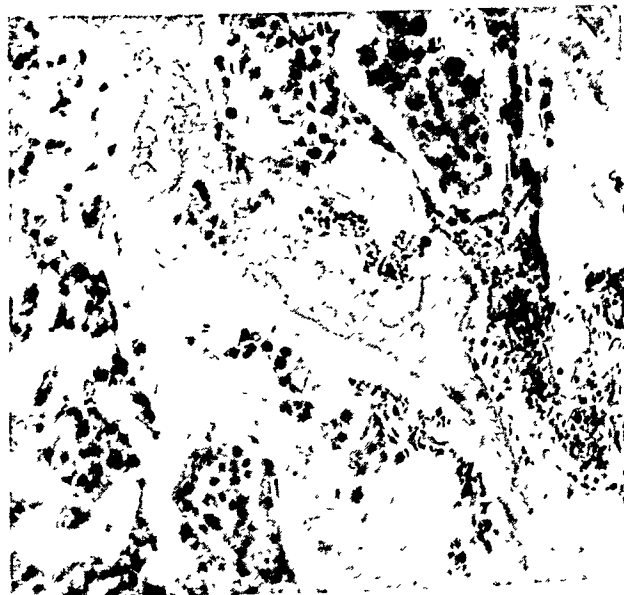
growth is rapid and malignant. Microscopically there is a good deal of resemblance to a fibrosarcoma of dense architecture comprising small, fusiform cells; these may lay down a good deal of hyalin matrix which may undergo calcification without, however, becoming ossified; osteoid tissue is the nearest approach to bone formation and very little of this may be produced. Metastases occur early and are widely disseminated throughout the body, so that here again early amputation is indicated.

Fibrosarcoma (Medullary and Periosteal) (Extraperiosteal Sarcoma). This has a much later incidence, being found after the thirtieth year. It affects the lower extremities, occurring at the lower end of the femur and upper end of the tibia but lying at a point where the shaft joins the lower or upper heads of these bones. Its rate of growth is slow. It may originate inside or on the outside of the bone, destroying the shaft and lifting off the periosteum as it grows. It is firm and fibrous and may be cartilaginoid. X-rays show the medullary type to be a sharply demarcated, more or less solid and opaque shadow, together with signs of an eroded and destroyed shaft; the periosteal type is dense and spares the shaft, while the shadow spreads into the soft parts.

Microscopically it is characterized by an excess of hyalin fibrous matrix over cellular components. Large fusiform cells lie in this matrix, which is decidedly avascular. Osteoid tissue and areas of calcification may be noted. Ewing considers this tumor to be mildly malignant and advises radiation by implication, as he states that many examples regress after this treatment. Geschickter and Copeland are in marked disagreement with this and give a poor prognosis; they advise amputation.

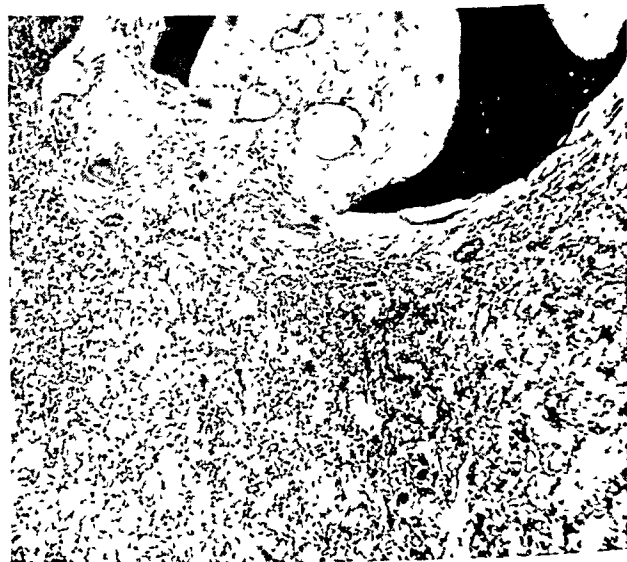
Other Malignant Tumors of Bone. Disregarding the rare liposarcomas which may develop in the bone marrow, we may proceed to those tumors which produce the majority of malignant lesions in bone as distinguished from those of bone: these are mostly carcinomas of a wide variety of

origins. The malignant myeloid tumors are discussed under the blood-forming organs. The breast, prostate, kidney, lung, uterus, and many other organs may contribute to



Bony metastasis of mammary carcinoma of solid canalicular type.

the long list of metastatic carcinomas involving bone. Some of these may emit a few metastases, like the clear-celled carcinoma of the kidney (hypernephroma); others may



Metastasis of a "hypernephroma" to bone. Large black structure at upper right and paler one to its left are surviving bony trabeculae which have not as yet been destroyed.

pepper the skeleton with metastatic foci, particularly the prostate, which has access to the vertebral column through the pre-vertebral plexus of veins described by Bat-

mentioned for the sake of recording it, as this term is often used by clinicians. Clinically there may be some difference in rheumatoid arthritis in different age groups, pathologically there is nothing to be gained by retaining these terms.

Summary The cause of this group of diseases is still debatable if not unknown

to say, without effect until an older physician has been called in consultation and recognized the disease for what it is. This amply indicates its present rarity.

Gout is a metabolic disease and is not necessarily connected with high alcoholic intake, although it usually is associated with high living and rich diets. It may be mono-



Section from gouty tophus of finger. Glandular appearance in lower left corner is attributable to macrophages grouped about masses of urates which have crystallized out in larger spaces in the field.

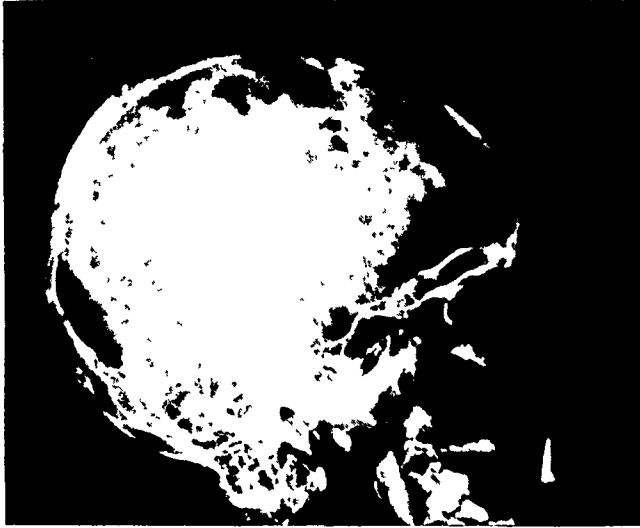
It is one of the major tragedies of medicine that so little progress has been made in this respect, for the more people that are spared to live through the roaring 40's, the more fall a prey to these arthritic maladies and reproach the physicians for knowing so little about them.

GOUT

In the days when life was more abundant and port wine more plentiful this was a common malady. One needs but to read the fiction of the Victorian age to realize this, nowadays it has happened that a patient with a typical gouty great toe has been treated for subacute infection by a surgeon without recourse to colchicine and, needless

or polyarticular, showing a particular fondness for the joints of the great toes and the fingers. It may be confined to the periarticular connective tissue, or it may involve the synovial membrane, the cartilage, and finally the bone, which may become extensively eroded and show striking changes in x-ray films. Not only articular cartilage may be affected, but that of the ear, as well. Urates are deposited in the tissue and hyperemia and inflammation ensue, or if the deposit of these salts is more gradual and less copious there may be simply fibrosis and a certain amount of distorting deformity and enlargement of the joints. If the lesion involves articular cartilage and bone

the granulation tissue that attempts to repair the lesion. Osteoid and osseous tissue may then develop in this granulation tissue, producing ankylosis, which immobilizes the joint. Subluxation of affected joints is not uncommon and results from the relaxation of the capsular ligament. As in rheumatic fever there may be fibrinoid degeneration of the connective tissue of the joint (already described in the section on vascular pathol-



Roentgenograph of skull in case of multiple plasmocytic myeloma. Note perfectly circular, punched-out areas in shadow of bone. (Col. F. H. Foucar)

ogy) and as in other rheumatic lesions there may be juxta-articular nodules (as described under "granulomas") formed near the joints.

Osteo-arthritis. In this disease the primary lesion appears to occupy the cartilage rather than the synovial membrane; sections from the center of an articular disc will show fibrillation of the matrix and hyalin softening of this substance. The chondrocytes may degenerate and disappear, or they may proliferate. The process results in an irregular "ulceration" of the cartilage which will produce much the same changes as one might expect in a rusty hinge; it grates, but it does not become ankylotic. The exposed bone at the base of the erosions in the cartilage becomes polished and eburnated, and the margins of the joint will show an overgrowth of the bone known as "lipping," with small stalactoid nubbins of

bone projecting in the form of osteophytes. Although the disease is not primarily synovial and proliferative, an outgrowth of villi may occur near the margin of the joint, and these may become detached and form the nucleus for "joint mice" after undergoing chondrification or ossification. These projections may be fatty and represent overgrowths of the normal "fat pads" of the joints. Here again one may observe juxta-articular subcutaneous nodules and, in the case of the fingers, "Heberden's nodes."

Chronic Infective Arthritis. This form of arthritis is associated with the "focal infections"—chronic inflammatory foci of a low grade that occur in the tonsils, at the apices of the dental roots, in the prostate, and possibly in other situations. The arthritis is usually polyarticular and may involve the spinal column, wrists, knees, ankles, and joints of the feet, as well as those of the fingers and hands. The fact that similar lesions can be experimentally produced by the injection of various cocci and that patients with this affection may respond well to the removal of infected teeth and tonsils or the injection of autogenous vaccines sets it off from the forms just described, which seem to be more stubbornly progressive. The pathology of the lesions is essentially that of osteo-arthritis and thus needs no further consideration.

Still's Disease. This is a chronic polyarthritis that is seen in children and rather closely resembles the rheumatoid form in the appearance of its pathologic lesions; presumably it represents that disease in a juvenile form. It is associated with enlargement of the spleen and lymph nodes, which merely show chronic hyperplasia, so that biopsies are of little assistance in arriving at a diagnosis. It may be said to have no distinguishing pathologic lesions; only the clinical picture separates it from rheumatoid arthritis.

Felty's Syndrome. Rheumatoid arthritis in young adults, accompanied by aplastic anemia and enlargement of the spleen and lymph nodes, goes under this name. It is

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it may produce ankylosis. The microscopic picture is not striking. Gouty tophi have been described under the granulomata.

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The fact that the thymus may be enlarged or the site of a tumor (usually nonmalignant "thymoma") may be ascertained only by appropriate operative procedures (See Thymus, p. 303.) The muscle may be flabby and show some atrophy, the only characteristic microscopic lesion is the presence of "lymphorrhages," which are more or less circumscribed collections of normal lympho-

seldom truly so. Miniature fibers may be found to measure as little as 1.5μ in diameter. The striking feature of the picture is that all these fibers, whether large or small, show well differentiated muscular cytoplasm with distinct striae and no signs of degeneration. The muscular nerve endings and spindles show no abnormality. There may be lymphocytic infiltration in the areas of



Field from biopsy of skeletal muscle affected with amyotonia congenita. Note large, sinuous, and normal fibers coursing diagonally across center of field and small "fibres en miniature" abutting on either side of them. These tiny fibers are pathognomonic of the condition.

cytes and resemble hemorrhages, but comprise these cells rather than erythrocytes. These may not be evident in every biopsy.

AMYOTONIA CONGENITA In this disease, which is congenital, there are fairly constant degenerative lesions in the anterior horn cells of the cord, so that there is evidence of its being a neuromuscular malady and the question of intra uterine poliomyelitis has been considered and rejected. The microscopic picture of a biopsy from a patient with this disease is striking and diagnostic: there are groups of miniature fibers from 3μ to 5μ in diameter lying intercalated between bundles of normal fibers 20μ to 50μ in thickness which may seem hypertrophic by comparison with the fibers "en miniature" (as they have been termed), but are

miniature fibers and there may also be fibrosis, but there is nothing like the lymphorrhages of myasthenia gravis.

Regeneration Biopsies may show areas of regenerating muscle that is very puzzling if one is unprepared for the microscopic pictures it presents. The nuclei become swollen and group themselves together, as a result of multiplication (possibly amitotic), to form masses that look very much like giant cells. In rather rare instances a few embryonal forms, granular and ovoid cells like "xanthoma cells," may be observed. They are an important link in our reasoning concerning myoblastic myomas, which will be discussed presently.

Inflammation ACUTE MYOSITIS This is a very common process in the neighborhood

Muscular and Adipose Tissue

MUSCULAR TISSUE

SKELETAL MUSCLE

HISTOLOGY

CONGENITAL ANOMALIES AND DEGENERATION

REGENERATION

INFLAMMATION

TUMORS

MUSCULAR TISSUE (*Continued*)

SMOOTH MUSCLE

ADIPOSE TISSUE

METABOLIC DISTURBANCES

ADIPOSIS DOLOROSA

TRAUMA AND INFLAMMATION

TUMORS

MUSCULAR TISSUE

There are three types of muscle in the body: the skeletal or striated, the smooth or nonstriated, and the cardiac, which combines the two. Cardiac muscle is not yet included in the material of the surgical pathologist to any appreciable extent.

SKELETAL MUSCLE

Histology. In brief, the skeletal muscle, which is the voluntary locomotive muscle of the human body, is composed of bundles of fibers, enclosed in sheaths of reticulum known as sarcolemma, and of cells that are essentially long, fusiform syncytia that are multinucleated, the nuclei lying along the surface of the syncytia. The fibrils that compose the fibers are marked by elaborate cross-striations, best seen in sections stained with phosphotungstic-acid hematoxylin and usually described as alternating groups of wide and narrow bands like those on the arm of a Naval lieutenant commander. These are subdivisible, but there is no need for going into that here.

Congenital Anomalies and Degeneration. Whole muscles or groups of muscles may fail utterly to develop, and there may be partial failures. Degenerative changes and necroses, such as Zenker's degeneration,

are of little importance in surgical pathology.

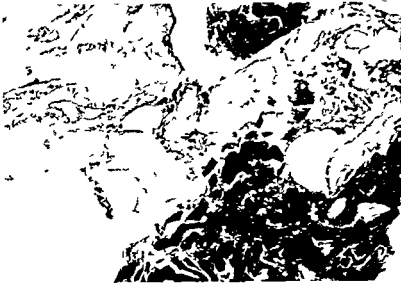
ATROPHY. Only specific atrophies interest us here, as these are often diagnosable through biopsies of muscle. Very little can be determined about a given muscle by gross inspection; muscular biopsies look very much alike even when there is a good deal wrong with this tissue. The microscope is invariably necessary in order to make a diagnosis.

JUVENILE PROGRESSIVE PSEUDOHYPERTROPHIC DYSTROPHY. This malady is familial and, as the formidable title infers, occurs in children. There is atrophy of some muscular fibers and hypertrophy of others, but the most striking lesion in a random biopsy is the replacement of the atrophic fibers by masses of adipose tissue which give the muscle a deceptively hypertrophied appearance and lend to a weak and helpless child a semblance of an overdeveloped and very muscular one.

MYASTHENIA GRAVIS. As one frequently receives biopsies from patients with this disease, a few words may be devoted to the characteristic lesion. The disease is one that concerns the physiology rather than the morphology of muscle, and the patient shows very little in the way of pathologic changes that may be observed in a biopsy.

vacuolization of the basal cells and areas of perivascular inflammation. The muscle shows a most interesting picture that may vary from a very mild myositis with perivascular lymphocytic exudate of a focal and scattered type to veritable muscular devastation, in which fibers not only have undergone cloudy swelling and degeneration but have actually become fragmented and necrotic. The lesion is not unlike that of the

muscle at its point of attachment to the periosteum, so that it is a rather natural sequence of trauma and is relatively unimportant. The generalized type is progressive, affects numerous muscles simultaneously, and begins in the aponeurosis and tendons, spreading into the bellies of the muscles and converting them into bony tissue. The myofibrillae lose their striae and disappear, to be replaced by fibrous tissue which, in



Bit of trapezius muscle from a focus of myositis ossificans. Note bony trabeculae and their fibrous marrow. Black areas represent overstained muscular fibers.

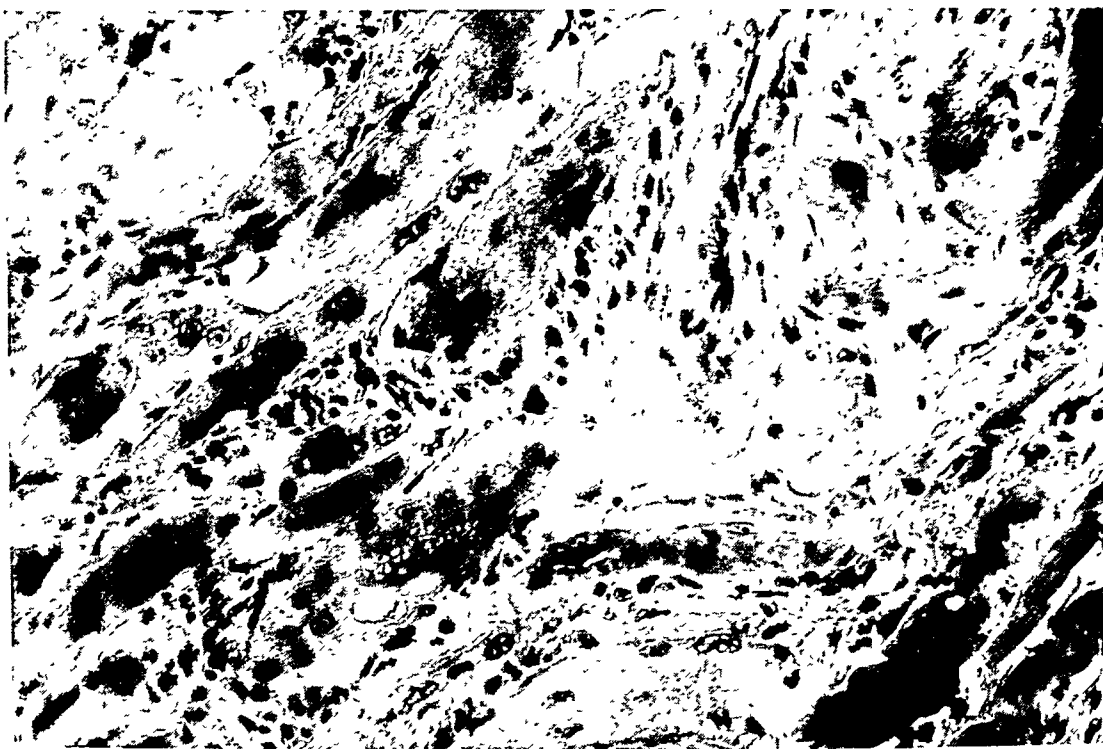
reaction to *Trichinella spiralis* (see p. 98), in fact the two may occur simultaneously. In that case one finds muscle that shows the very marked lesions just described, with out any trace of the presence of trichinella past or present and, in other parts of the body, typical infestations by the larvae of this worm. Such mixed cases are most perplexing.

MYOSITIS OSSIFICANS There is a chronic fibrous myositis, which we may mention in passing, it is a rather banal chronic inflammation of muscle that interests the patient far more than the pathologist, as it may be very painful and cause much "stiffness" and inconvenience. Much more interesting is myositis ossificans, in which there are two forms: localized and generalized. The former is usually due to trauma to

turn, becomes ossified with or without an intermediate cartilaginous phase. The etiology of this disease is conjectural.

TRICHINOSIS The worm that causes this disease lives in the intestines of rats and swine and would probably confine its life cycle to these animals if we did not eat them. Underdone or raw meat from the swine, whether smoked or not, can contain the parasitic larvae of trichinella, which are usually detected in inspected meat, but may escape the eye of the inspector. A man eating such meat will run no risk if the meat is thoroughly cooked but if it is underdone he becomes infested by the larvae that are set free in the intestine when the meat is digested.

Transient bouts of fever, nausea, and diarrhea herald this event. In about two



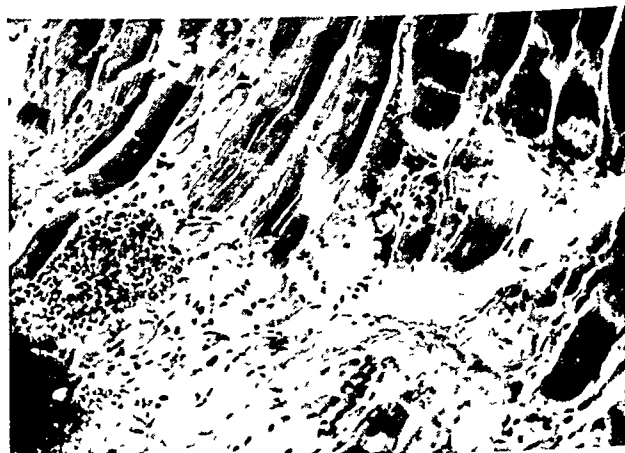
Regenerating skeletal muscle in a focus of hemorrhagic necrosis of rectus muscle—a not uncommon lesion but of obscure origin.

of such inflammatory lesions as carbuncles, appendiceal abscesses, and similar processes. Abscesses of muscle may complicate an infectious disease elsewhere in the body; they are seen in connection with typhoid fever, when they are caused by the typhoid organisms; they may also be produced in acute pyogenic infections and infectious diseases of an exanthematous type. There is no need to go into detail, as the lesions are those of acute inflammation in any tissue: leukocytic infiltration, edema, precipitation of fibrin, and necrosis.

ACUTE POLYMYOSITIS. This may follow acute infectious disease or may develop independently as small lumps or nodules in such muscles as the gluteus medius, or there may be more generalized areas of myositis with fever and even fatal termination in case the diaphragm should become involved. Under the microscope nothing very unusual meets the eye; there is edema, some fibrin has been deposited in the tissue, and there is some albuminous degeneration of the myofibrils with an occasional scattered hemorrhage.

DERMATOMYOSITIS. This is becoming the bane of the surgical pathologist, as its pres-

ence is often suspected by the clinician and its lesions are not often demonstrable in the muscle and skin sent in for pathologic



Muscular lesion in dermatomyositis. Note perivascular collection of lymphocytes (resembling a "lymphorrhage" in myasthenia gravis) adjacent to area of hemorrhage in lower left corner. There is an increase in number of muscular nuclei here and there, indicating proliferative regeneration.

examination. It is a generalized disease akin to disseminated lupus erythematosus and polyarteritis nodosa. The dermal lesions will be discussed in the section on the skin; they consist of thinning of the epidermis with

vacuolization of the basal cells and areas of perivascular inflammation. The muscle shows a most interesting picture that may vary from a very mild myositis with perivascular lymphocytic exudate of a focal and scattered type to veritable muscular devastation, in which fibers not only have undergone cloudy swelling and degeneration but have actually become fragmented and necrotic. The lesion is not unlike that of the

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Transient bouts of fever, nausea, and diarrhea herald this event. In about two

days the larvae mature and set about reproducing themselves, the adult females giving birth to thousands of larvae which then gain access to the circulation via the intestinal wall. These then settle down in the muscular fibers, having penetrated their sarcolemma. Such larvae are at first straight and lie parallel with the axis of the fiber;

soreness, and a fever that may attain 40° C. or more. There is apt to be edema of the periorbital tissue about the eyes; the blood usually exhibits intense eosinophilia.

With an antigen prepared from trichinella, one may obtain agglutinations and skin tests, as the presence of the worm sets up a distinctly allergic reaction. *Trichinella* may



Small segment of larval trichinella in its vacuole in a shred of deltoid muscle. It has not yet coiled and is surrounded by inflammatory exudate (center). Note large sarcolemmal nucleus to right of worm; sarcolemmal elements will aid in forming wall of cyst.

as they grow they coil within the muscle and a wall is formed about them which is, for the greater part, composed of sarcolemma and shows swollen nuclei in clumps. These are hyperchromatic and resemble those of regenerating muscle; as the worms cause degeneration and necrosis, this is probably a regenerative reaction even so. As time goes on the wall of the cyst becomes increasingly fibrous and eventually calcifies. Muscle in the neighborhood of the invaders shows hyalin swelling and necrosis, and there is apt to be a brisk exudation of leukocytes in the immediate vicinity of the cyst. During this process the host undergoes a "rheumatic attack" with marked muscular pain,

invade cardiac muscle, and I have seen it invade the smooth variety in a patient with metastatic leiomyosarcoma with multiple metastases, many of which showed the parasites. (This was a "cause célèbre" of Dr. Frank Mallory's.)

The favorite muscles for infestation are the diaphragm and the muscles of the eyes, both of which are obviously unsuitable for biopsy; it is usually satisfactory to take a biopsy from one of the accessible aching muscles; if none seems to be particularly involved the deltoid or gastrocnemius makes good material. Gross examination of the specimens is seldom very productive, as most of the biopsies are taken before the

cysts become macroscopically visible. In the later stages a sharp eye may detect the small calcified cysts as tiny whitish yellow specks in the muscle, particularly after this is crushed between two glass slides where it may be examined with a hand lens. As a rule it is better to make a series of twenty or more serial sections from the biopsy and examine all of them if larvae are not evi-

seen in children. Simple excision is the treatment of choice.

MALIGNANT For a long time the rhabdomyosarcoma was recognized as a variety of teratoid tumor that occurred about the vagina and cervix of young girls ("sarcoma botryoides") or in the endometrium of older women. The work of Fujinami proved that they could also be found in skeletal muscle



Nonmalignant rhabdomyoma from leg of child of 12. There is some grouping of neoplastic cells into thick bundles, and the tumor is quite dissimilar in its appearance from malignant variety.

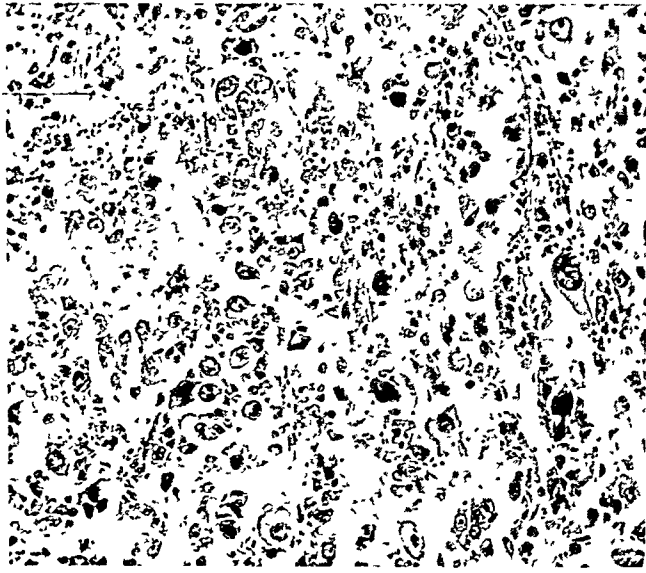
dent in the first two or three. Lesions of polyarteritis nodosa and dermatomyositis may simulate those of trichinosis, and one can often be misled by this likeness.

Tumors of Muscle NONMALIGNANT The myoblastic myomas or myoblastomas are only beginning to be recognized. They are yellowish, fleshy tumors that are most often found in the tongue, neck, or extremities. Their appearance simulates xanthoma both macroscopically and microscopically, although some of them may exhibit alveolar grouping of the cells or more formidable-looking tumors that suggest rhabdomyosarcoma at first glance. The pseudoxanthomatous type may occur at any age, the more obviously rhabdomyoblastic variety is often

where they arise spontaneously from the muscle itself, replacing it within its sheath. Such tumors are soft and encephaloid, and after biopsy they tend to grow out into fungating masses of brain like tissue in the surgical dressing. Therefore it is well to plan for a radical operation shortly after the intended biopsy is scheduled.

The microscopic appearance of this tumor is very characteristic, and for some obscure reason it seems more often to be misdiagnosed than other tumors. It is composed of two types of cell: a large and spectacular giant cell that exhibits a few beaded fibrils within its cytoplasm and may have several nuclei, and a small, fusiform, or strap-shaped cell that may or may not exhibit

exquisite cross-striations in its cytoplasm. The nuclei of both varieties are very large, vesicular, and marked by a coarse karyoplasm; they have large, fuchsinophil nucleoli.



Rhabdomyosarcoma of tibialis anterior. Nuclei of cells of this tumor are quite characteristic. Cross-striations, found elsewhere in tumor, are not visible in this section. Patient alive and well ten years after amputation at mid thigh.

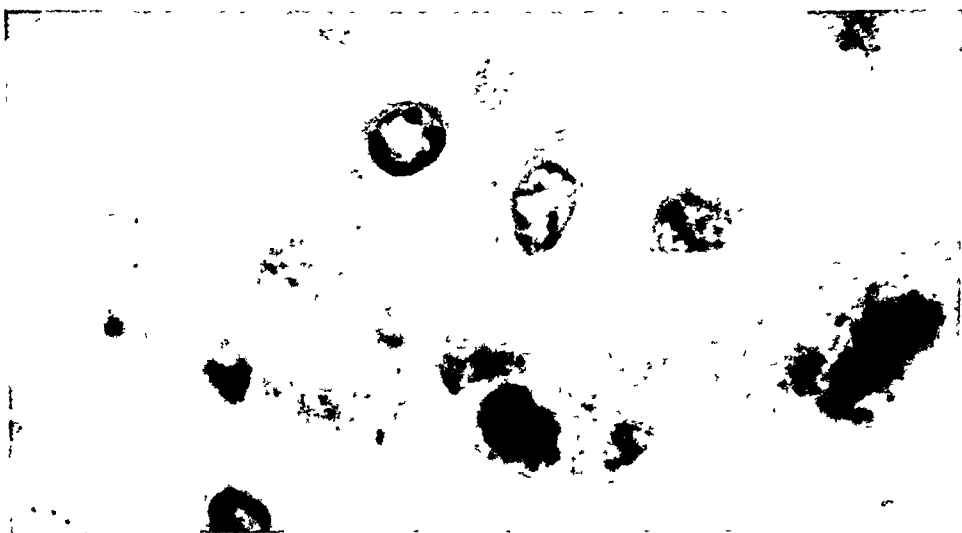
It is just as well not to insist on the presence of cross-striations as a necessity for a positive diagnosis; while they are plentiful in the better-differentiated tumors, they are often difficult to find in the wilder, more metaplastic varieties, where they may

be entirely lacking. The striations are not at once developed in the embryo, and there is no reason why a malignant tumor should not, in its type, antedate the period at which these first appear; if this occurs the striations are lacking. They seem to appear more regularly in those rhabdomyosarcomas which develop ectopically than in those which arise in skeletal muscle, which is paradoxical to say the least. The peculiar combination of fusiform and giant cells with very striking nuclei having coarse karyosomes and large nucleoli is seldom if ever seen in other tumors save the choriocarcinoma and the most metaplastic varieties of pleomorphic bronchogenic carcinoma.

If these rhabdomyosarcomas are removed before metastasis has occurred there is a chance of curing them; surgery is the best resort, and if they arise in an extremity, amputation is indicated. Usually they are not safe to leave alone, being very malignant. In the uterus they may be discovered accidentally at autopsy, having been unnoticed before by the patient or her physician. This, however, is unusual.

SMOOTH MUSCLE

This is so much a part of organs to which it imparts motion of one type or another that it cannot well be discussed alone. Its lesions are those of the organ in which it is



Gigantic cell in rhabdomyosarcoma of uterus. Oil-immersion photomicrograph. Note cross-striations throughout its cytoplasm.

found, and its tumors will be taken up in connection with the uterus, prostate, and alimentary tract, where they most often are



Leiomyoma of gastric wall. This is almost purely muscular and so orderly that it might be mistaken for normal musculature. (Compare with fibrous leiomyoma [fibroleiomyoma] of uterus, which is quite different.)

found. Tumors of smooth muscle in the skin will be considered in the section devoted to that tissue.

ADIPOSE TISSUE

This is almost as widely distributed in the human body as is connective tissue of the collagenous variety; it forms considerable masses which constitute the "pin-nucleus adiposus" of the subcutaneous tissue. Its functions are to isolate the body from thermal changes and to serve as a storage reservoir of hydrocarbons. It is concentrated in the internal parts of the body in the neighborhood of organs, particularly the kidney, for which it forms capsules of fat, and the intestines. The omentum is essentially an apron of peritoneum laced with fatty tissue.

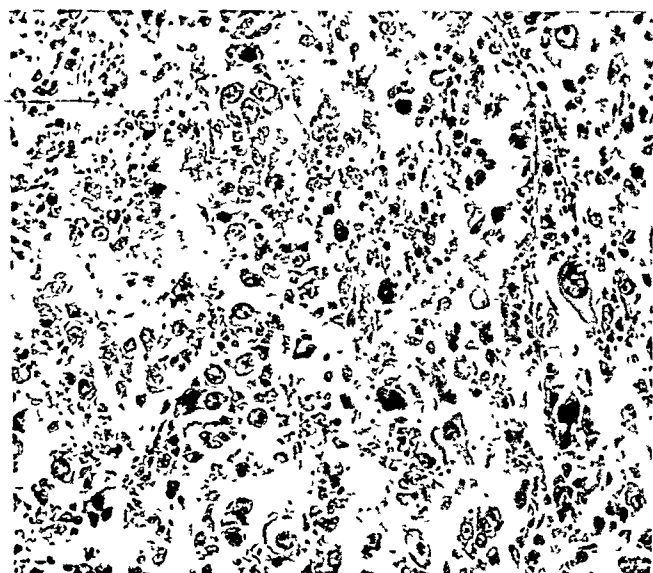
Metabolic Disturbances. Obesity is too well known to merit very much discussion here, and it seldom constitutes a surgical problem excepting when it figures in plastic surgery. Here the surgeon may reduce the size of pendulous fatty pads, "double chins,"

and the like. Fat is not visibly different from normal tissue. Occasionally one encounters local hypertrophy of fat in the form of overgrowing masses that have the appearance of normal fat and not the opaque, somewhat granular and laminated arrangement of the true fatty tumor or lipoma. Obesity is usually connected with hormonal disturbances; in these pages it is spoken of in connection with lesions of the pituitary gland and with certain tumors. As Boyd points out, Dickens' well-known fat boy Joe was undoubtedly created upon the basis of a sufferer from Frohlich's syndrome.

Adiposis Dolorosa. There is another type of obesity that goes under this name and differs from generalized obesity in that it is localized in the face, breasts, abdomen, and the upper arms and thighs, sparing the arms and legs with their extremities. The adipose deposits in this disease may be exquisitely sensitive and painful, hence the adjective "dolorosa." The disease, first described by Dercum, accompanies tumors that impinge upon the pituitary and is usually associated with pathologic changes in the glands of internal secretion. The thyroid shows sclerosis, the suprarenals may show uni- or bilateral adenomas of the cortex, or merely hyperplasia, the gonads may be atrophic or "defective." A subject upon whom the writer performed an autopsy showed two malignant meningiomas, one of which impinged upon the hypophysis and compressed it.

Trauma and Inflammation. The adipose tissue is readily traumatized, particularly in the breast, and such trauma may lead to foci of necrosis in which the fatty cells are "exploded," their oily contents being dispersed and taken up by fat phagocytes which form a hard, compact mass that is usually pearly white or light yellowish and rather soapy and opaque. Fat necrosis that is due to the extravasation of pancreatic ferments in pancreatitis has much the same appearance, excepting that the microscope shows a more active leukocytic (polymor-

exquisite cross-striations in its cytoplasm. The nuclei of both varieties are very large, vesicular, and marked by a coarse karyoplasm; they have large, fuchsinophil nucleoli.



Rhabdomyosarcoma of tibialis anterior. Nuclei of cells of this tumor are quite characteristic. Cross-striations, found elsewhere in tumor, are not visible in this section. Patient alive and well ten years after amputation at mid thigh.

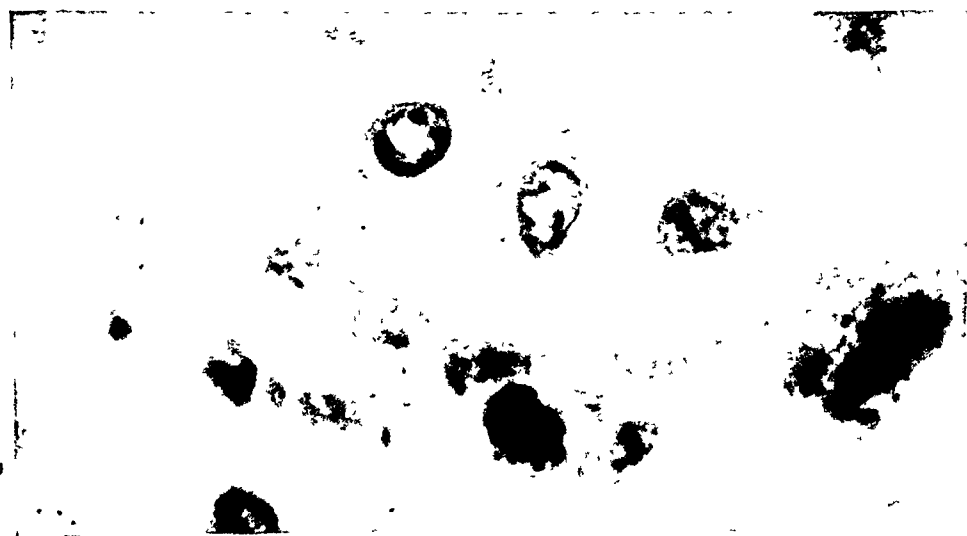
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SMOOTH MUSCLE

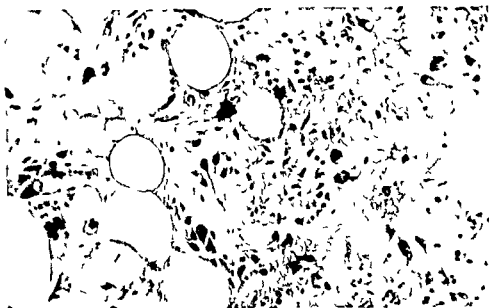
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Gigantic cell in rhabdomyosarcoma of uterus. Oil-immersion photomicrograph. Note cross-striations throughout its cytoplasm.

type, which is confusing as it appears to reverse the actual appearance of the tumors. The first is composed of embryonal or metaplastic cells, while the second is made up of well differentiated fat in which poorly differentiated mucoid elements supply the sarcomatous features. Possibly one might avoid confusion and hair splitting by calling them respectively "liposarcoma" and "intermuscular myxoliposarcoma."

scale is a tumor composed of metaplastic cells of all sizes and shapes that show vacuolization, the vacuoles revealing lipid content when properly stained. In such tumors giant cells and grotesque forms are not unusual. This type is often found near the kidney, but liposarcomas may occur anywhere that lipomas may arise. The tumors are best treated by surgery and offer little allurements to the roentgenologist.



Myxolipomatous form of liposarcoma in which fat is approximately normal but is invaded by mucoid tissue containing bizarre, arachnoid giant cells that typify the tumor.

True Liposarcoma This tumor is characterized by being yellow and opaque and by showing a distinct tendency to break down and cause extensive hemorrhage into its substance, particularly when it arises in the perirenal capsule. Its microscopic picture varies; it may be a fairly orderly tumor composed of alveolar groups of oat-shaped cells containing very fine granules of fat that are demonstrable only by the use of appropriate stains, such as sudan III, and are entirely unnoticeable in sections stained by ordinary techniques. They show active growth and some invasive propensities. Among the very immature cells just described a little searching will reveal a few "mulberry cells." The other extreme of the

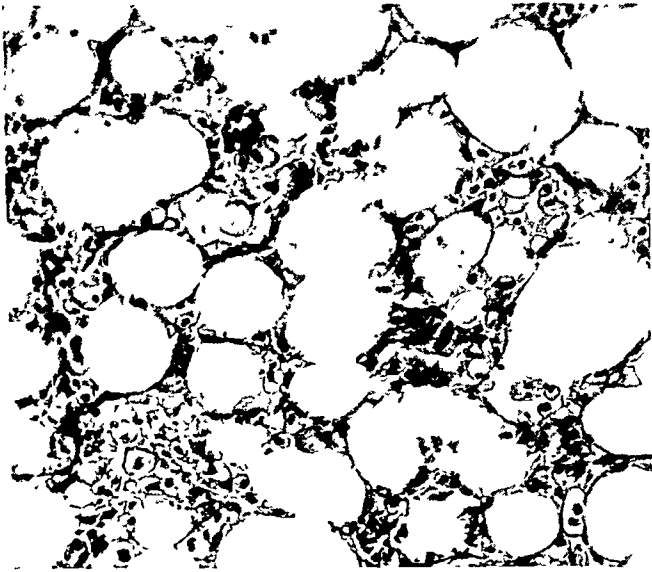
The prognosis in these liposarcomas is somewhat variable. It is best to consider them malignant and advise the surgeon accordingly. The more cellular the sarcoma and the less fat it contains the more malignant will it be, therefore compact, cellular, and comparatively nonfatty liposarcomas carry a poor prognosis.

Intermuscular Myxolipoma This tumor is apt to be globular, well encapsulated, and very firm, rather than soft and compressible like a lipoma. On section it is much like that tumor excepting that its section surface drips mucoid fluid. It is found between muscles, attached to thick fascial sheets like the fascia lata and other such structures.

Its microscopic picture is similar to that

phonuclear) infiltration and there are extensive hemorrhages.

A febrile inflammation of the fatty panniculus, known as "nonsuppurative nodular panniculitis," has been described by Weber and Christian and is occasionally encountered in biopsies. In this disease there are multiple foci of acutely inflamed, painful, and tender fat that form small nodular



Section through area of simple necrosis of adipose tissue. The clusters of small cells with granular cytoplasm are phagocytes that have taken up necrotic fat. There is little else to be noted.

masses beneath the skin. After the disease subsides, these undergo fibrosis and leave characteristic linear and branching lesions that feel like twigs embedded beneath the skin. The microscope reveals a typical area of fatty necrosis with accompanying acute inflammation and possibly slight hemorrhage. The older lesions exhibit extensive fibrosis of the fatty tissue. The cause of the disease is not yet known.

Tumors of Adipose Tissue. NONMALIGNANT (LIPOMA). The lipoma is a tumor composed of adipose tissue and it is usually so characteristic as to need no microscopic confirmation of the diagnosis. On gross examination it may lie buried in other tissues, but it often arises subcutaneously and pushes itself outward into a pouch of thin skin which covers it. It is pendulous and

pedunculated, in this case, and soft in texture. When removed, these tumors are very apt to show a fatty core that may be milky white or may be yellow and fairly translucent. The deeper variety is usually scalloped at the margin and may resemble a boxing glove or a catcher's mitt; or there may be a number of grotesque projections of a lobular nature from a fatty center. The fat is usually arranged in concentric lamellae a few millimeters in thickness. These tumors also arise in the omentum, from the fat of the appendices epiploicae and other such structures; in this case they interfere with peristalsis, or they may compress soft organs like the lungs. When found in the thorax they are often combined with mucoid connective tissue which has a common embryologic origin with them, so that myxolipomas are somewhat more common in the mediastinum than are pure lipomas. They may attain huge proportions; the author has seen one that filled the entire pleural cavity on one side and caused complete compression of the lung. Such tumors weigh over a kilogram.

The microscopic appearance of a lipoma is usually indistinguishable from that of normal fat, and it seldom pays to examine such tumors microscopically unless they show some gross peculiarity to indicate that they are out of the usual run. There is a type of lipoma that is composed in large measure of embryonal "mulberry cells"—fat cells with a central nucleus that is surrounded by a cluster of fat droplets enclosed in vacuoles. These are probably not to be considered as liposarcomas but rather as an immature variety of lipoma, as they exhibit no invasive growth and show no mitotic figures; they are known as "embryonal lipomas."

MALIGNANT (LIPOSARCOMA). There are two types of liposarcoma, one of them a pure form found in situations where fat is indigenous and the other a mixed mucoid type usually found in fascial planes and intermuscular septa. Ewing calls the former the "adult" and the latter the "embryonal"

8

Serous Membranes

RECOGNITION OF CELLULAR ELEMENTS
HISTOGENESIS AND HISTOLOGY
INFLAMMATION (SEROISITIS)

BURSITIS AND GANGLIA
TUMORS

Formerly the linings of the pleural, pericardial, peritoneal, and other serous cavities like joints and bursae were all considered as "endothelium", today we speak of "mesothelium" because these membranes are formed from the mesoderm and do not line vessels, the lining of which is endothelium in its proper sense. Whenever such membranes are irritated or inflamed, or when an imbalance in the fluids of the body produces edema, the mesothelium lined sacs accumulate liquid. The simpler pathologic conditions depending upon passive congestion and edema produce "transudates" of low specific gravity (1010) which are so much like water that they are called "hydropic," and one speaks of "hydrothorax" or "hydropericardium." Under conditions of inflammation, however, they are no longer simple transudates, but become exudates and contain albumin and even cellular elements and fibrinogen that may cause clotting after they are drawn off into glass containers. Such exudates have a higher specific gravity (1020+).

The surgical pathologist can tell a good deal about the cause of such fluid accumulations by ascertaining the specific gravity and allowing the sediment to precipitate by gravitation. Then, by centrifugating the resulting concentrate after decanting the supernatant fluid, he may fix such precipitates in formalin or any other fixing fluid, and the resulting button may be removed from the centrifuge tube and embedded in paraffin.

It is then sectioned, stained, mounted, and examined. This process is familiarly known as making a "cell block examination," and it can be very useful.

Bloody fluids may indicate tuberculous inflammation or the presence of neoplastic metastasis in the mesothelium, those that show a large percentage of lymphocytes and monocytes (about 75 per cent or over) will probably prove to be tuberculous, those revealing large numbers of immature leukocytes of various descriptions will indicate some variety of leukemia, and, finally, those showing actual fragments of tumor, or many atypical cells, will point to the presence of metastases in the mesothelium. Such examinations may be carried out on any fluids that are amenable to centrifugation, such as pleural, pericardial, or ascitic effusions, together with fluids from joints, but any material that contains mucus will prove to be refractory. Sputum and gastric contents, or vomitus, are very unpromising for "cell block" determinations and should not be accepted for such examination. The mucus makes it impossible to centrifugate the specimen, and any measures taken to liquefy the mucus will interfere with good histologic stains.

RECOGNITION OF CELLULAR ELEMENTS

Naturally, leukocytes, erythrocytes, and monocytes are readily recognized, but it takes a little practice to be sure of meso-

of an ordinary lipoma. Scattered here and there one may find groups of mulberry cells, but the general appearance of the tumor is strikingly orderly and ordinary until one notices that there are numbers of large, very atypical cells like those of a fibrosarcoma scattered throughout the fatty tissue. These vary from somewhat overgrown fibroblasts, with hyperchromatic nuclei and a fusiform or gourd-shaped cytoplasm, to peculiar multinucleated giant cells that differ from ordinary foreign-body syncytia in that they have fewer, more hyperchromatic nuclei and possess peculiar processes like spider legs that radiate from the cytoplasm into the stroma. At first glance one might interpret the tumor as a lipoma in which the fibrous stroma was undergoing sarcomatous change, and this might come fairly close to the actual state of affairs in this tumor. The large cells often show lipid granules in their cytoplasm. Ewing considers them to be derivatives of myxoblasts. This tumor is possibly of a much lower degree of malignancy than is the liposarcoma proper, but Ewing states that it tends to recur after removal and to become more malignant with each recurrence until metastasis ends the patient's career. Its prognosis, then, is better than that of the true liposarcoma. Surgical treatment should be thorough, and care should be exercised to remove the tumor completely with the underlying fascia to which it is attached and from which it presumably takes origin.

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It should be stressed that negative diagnoses reading "no neoplastic cells found"

HISTOGENESIS AND HISTOLOGY OF SEROUS MEMBRANES

The membranes lining the pericardial, pleural, and peritoneal cavities develop from mesenchymal tissue which, in turn, is derived from the mesoderm. Clefts appear in the diffuse masses of mesenchyme and develop into cavities that are lined by squam-



Section through a subsidiary cyst in a cyst of canal of Nuck. This bears extraordinary resemblance to a ganglion of tendon sheath in chronic tenosynovitis. Note mesothelial cells forming lining and occasionally piled up into several layers.

are of little value in and of themselves, they merely indicate that there is no active casting off of neoplastic cells from the serous surface at the time of the diagnostic tap, and they do not exclude the presence of a malignant tumor. The positive diagnosis, on the other hand, may be invaluable in clinching a clinical diagnosis. Use of this method should be encouraged a little experience on the part of the pathologist, with frequent recourse to the determination of the n/N ratio while he is learning to recognize neoplastic cells, will soon enable him to make valuable contributions to the diagnosis of these cases.

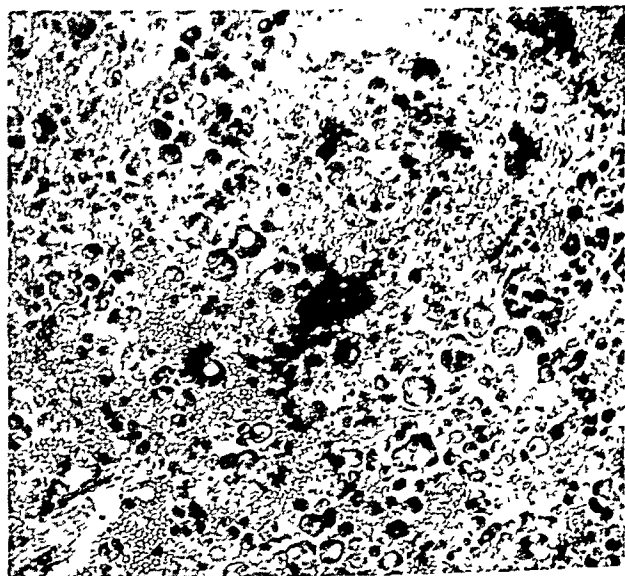
ous cells known as "mesothelium." Not dissimilar is the mode of production of the cavities of joints, but there is some controversy as to the nature of their lining. Prentiss and Arey speak of the synovial cells as "epithelial", Stohr mentions that there is a double layer of "epithelial cells" covering the synovial villi, Strong and Elwyn call these elements connective tissue cells that exhibit "epithelioid" characteristics, while Maximow and Bloom state categorically that they are fibroblasts which have adapted themselves to function as a cellular lining and that they are not epithelial at all.

thelial cells. These cover the inner surface of the serous membranes and may desquamate into the fluids that they secrete; in cirrhosis there is an enormous desquamation of mesothelial cells from the peritoneum into the ascitic fluid. As a corollary, there must be an equally vigorous production of these cells to bring this about. This appears to take place largely in the lower pouches of the peritoneum: the cul-de-sac of Douglas and the rectovesical pouch. Here, if one examines the region carefully, one may find a heaping-up of the mesothelial elements into villous masses.

The mesothelial cells are polygonal, dense elements that tend to have somewhat hyperchromatic nuclei, so that they are readily mistaken for epithelium. Their nucleoli, however, are small and inconspicuous, and there is apt to be a peripheral zone of small vacuoles suggesting abortive intercellular bridges in the marginal cytoplasm of the cells. Furthermore, they may show a certain amount of concentric lamination of their cytoplasm. In order to differentiate them from neoplastic cells it is sometimes necessary to measure the longest diameter of the nuclei and of the nucleoli of a series of cells (say ten or twenty) and average these. When the average of the nucleolar measurements is divided by that of the nuclear a figure known as the nucleolo-nuclear ("n/N") ratio is obtained. Most fluids show cells with a ratio below 0.20 when no tumor is present and one of 0.25 to 0.40 when neoplastic cells are represented; the ratios between 0.20 and 0.25 constitute a transitional zone where one must always be uncertain. There is reasonable assurance that neoplastic cells are being dealt with when: (1) there are fragments of tumor with its stroma present in the fluid; (2) the n/N ratio ranges above 0.30; and (3) the measurements of the diameters are extremely variable, which connotes a corresponding variability in the over-all diameters of the cells themselves. It should not be understood that the high n/N ratio

is of itself pathognomonic of neoplastic cells; it merely so happens that most metastatic tumors that invade serous membranes are carcinomas, and these comprise cells the nucleoli of which are always larger than are those of mesothelial elements.

The observance of multinucleated cells or of mitotic figures is of little significance, particularly if the latter are well formed;



Section from sediment of pleural fluid showing massive deposits of neoplastic cellular complexes that indicate carcinomatous origin but do not betray original site of carcinoma.

these phenomena may be observed in mesothelial cells which are multiplying in the serous fluid like bacteria in a culture medium. Nor is the presence of fibrin or of erythrocytes of much assistance; very often some blood is drawn into the tap as a result of trauma to vessels. One may very occasionally find fragments of liver in sediments from thoracic taps! The reason for this is obvious: the needle has been introduced too low on the chest, or the liver may lie unusually high.

Large numbers of mesothelial cells are found in ascitic fluids and in thoracic fluids from patients suffering respectively with cirrhosis and congestive heart-failure. Strangely enough, actual acute peritonitis or pleuritis may produce very little mesothelial desquamation. It is often maintained

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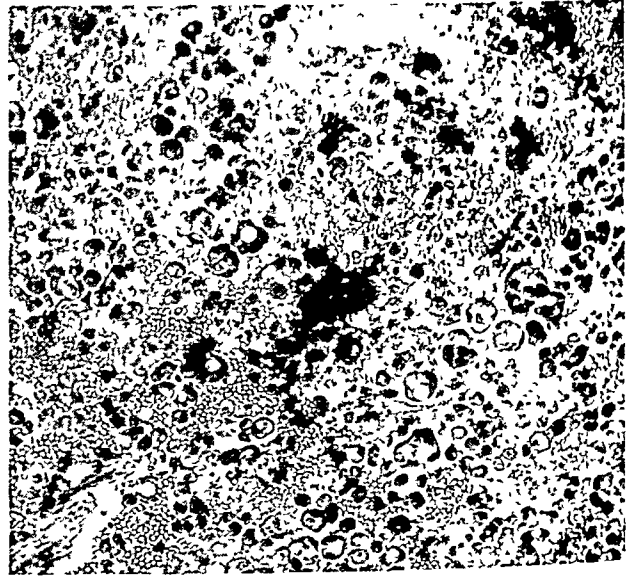
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because the amalgamation of the heart with the pericardial sac limits its motion, particularly its expansion. As time goes on the organ becomes covered with a dense leathery membrane that represents a "desmoid" variety of fibrosis. Under such circumstances surgeons frequently denude the heart of the covering layer of leathery pericardium. Examination of this is not at all exciting but

are known as "milk spots" or "patches", over the spleen and liver they give the effect of being coated with sugar frosting or icing. This was called "Zuckerguss" by the German pathologists, and in our language that term is generally used without being translated. (If one does use it one should pronounce it correctly and not say "zooker-goose," but "tsukerguss," with the u like



Calcified area in adhesive pericarditis, dark half of picture is calcified connective tissue which has caused scratches in the section. There is a small island of calcified tissue in the inert, paler fibrous tissue in the field.

it reveals ample cause for the cardiac embarrassment occasioned by its presence. There is a mass of dense fibrous tissue like that of a ligament ("desmos") in which one may find plaques of calcium carbonate or phosphate. It is almost impossible to determine where the pericardium proper ends and the organized intrapericardial exudate begins, so intimately are they intermingled.

FIBROUS SEROSITIS. After a period of chronic inflammation any of the serous membranes may become thickened and milky white, forming a dense and inflexible layer of almost cartilaginous consistence upon the surface of the membrane. In many instances this occurs on the visceral surface of an organ and produces irregular, thick, white plaques. In the case of the heart these

the double o in "foot" or the u in "pull"). The process is of no surgical importance, but it should be recognized when it is encountered in laparotomies. Calcification of such patches is not unusual.

INFECTIOUS GRANULOMA. Tuberculosis. Tuberculosis often affects the serous membranes in the form of tuberculous pleuritis, pericarditis, and peritonitis, and as tuberculous arthritis. In the pleura it is associated with fibrosis and usually with extensive caseation and tuberculous empyema. In the peritoneum it is less apt to occasion thick fibrinous and fibrous inflammatory reactions, but it excites a serous exudate which is very apt to be bloody. The peritoneum is found to be covered with milium tubercles like small translucent beads. It

It is only when one has to do with tumors of these membranes and is called upon to explain their glandular appearance (exhibited alike in those of the pleura and peritoneum) that one begins to ponder over these somewhat varying theories. As regards the synovial membranes, the concept that their lining cells represent adapted fibroblasts would pass unchallenged under the ordinary conditions of health and inflammation, for it is very difficult to demonstrate a convincing "epithelial" lining in joints and bursae unless certain chronic inflammatory processes or tumors bring them to light.

PATHOLOGY

Inflammation. It is most profitable to consider inflammation of the membranes in one section, as it does not differ very noticeably in the various subdivisions, such as pleura, pericardium, or peritoneum.

ACUTE SEROSITIS. Acute inflammation seldom concerns the surgical pathologist, as acutely inflamed serous membranes are not removed. One often finds acute inflammation in the sacs of hydroceles which presents minor peculiarities. The sac is developed as an offshoot of the peritoneum and therefore technically suffers from a form of localized peritonitis when it becomes inflamed. During the process the fibrin that is formed tends to become rolled into small pearl-like pellets that later undergo organization and acquire a glistening, iridescent outer coating of compact fibrous tissue. Should the fluid from such an inflamed sac be sent to the laboratory it will be found to contain fibrin and pus. Acute inflammation of the synovial membranes is of more clinical than surgicopathologic interest; it is discussed in connection with arthritis (see p. 90). The tendon sheaths undergo acute inflammation or "tenosynovitis," which may be dismissed with mention; it is the subacute and chronic forms that interest us here.

SUBACUTE SEROSITIS. While examining the sediments of serous fluids one is often struck with the large number of leukocytes that one may obtain by centrifugating slightly

turbid specimens that would not be expected to yield so many. There is a good deal of subacute peritonitis in connection with ascites, particularly in the case of patients who have been repeatedly subjected to tapping; subacute inflammation may persist in the pleural cavity after pleuritis or empyema.

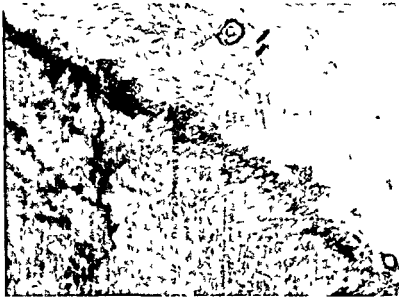
CHRONIC SEROSITIS. NONSPECIFIC TYPE. Serous membranes may become chronically inflamed for a number of reasons, the inflammation usually being secondary to one in an underlying or neighboring viscus. This may lead to several complications.

Adhesions. After acute inflammation has evoked an exudate of fibrin upon the surface of a serous membrane and the process begins to subside, this fibrin is rolled or pulled into bands and cords which are then organized by fibroblastic and vascular invasion. Sometimes whole sheets of fibrin become organized into fibrous sheets, and it sometimes happens that an entire cavity will be obliterated by masses of organized fibrinous exudate. These masses of newly formed fibrous tissue are known as "adhesions," and their formation when they are not wanted and lack of formation when the surgeon wants them are notorious features. Nobody can predict when they will or will not certainly be produced; as a rule, the cleaner and more skillful the technic of the surgeon (including his skill with sharp dissection) the fewer will be the adhesions. Contrarily, the more the surgeon indulges in blunt dissection, the more he tears and sponges the operative site, the more chances will he create for the formation of adhesions. As a result of acute inflammation chronic fibrous adhesions may set up barriers that will limit the spread of the infection which may continue in a subacute form within their confines, sometimes as a subacute abscess.

CHRONIC ADHESIVE SEROSITIS. We have hinted at this in the case of the pleura, where the lungs may become united to the thoracic wall by firm fibrous adhesive sheets. In the pericardium this is a very serious matter

because the amalgamation of the heart with the pericardial sac limits its motion, particularly its expansion. As time goes on the organ becomes covered with a dense leathery membrane that represents a "desmoid" variety of fibrosis. Under such circumstances surgeons frequently denude the heart of the covering layer of leathery pericardium. Examination of this is not at all exciting, but

are known as "milk spots" or "patches", over the spleen and liver they give the effect of being coated with sugar frosting or icing. This was called "Zuckerguss" by the German pathologists, and in our language that term is generally used without being translated. (If one does use it one should pronounce it correctly and not say "zooker goose," but "tsukerguss," with the u like



Calcified area in adhesive pericarditis, dark half of picture is calcified connective tissue which has caused scratches in the section. There is a small island of calcified tissue in the inert, paler fibrous tissue in the field.

it reveals ample cause for the cardiac embarrassment occasioned by its presence. There is a mass of dense fibrous tissue like that of a ligament ("desmos") in which one may find plaques of calcium carbonate or phosphate. It is almost impossible to determine where the pericardium proper ends and the organized intrapericardial exudate begins, so intimately are they intermingled.

FIBROUS SEROSITIS After a period of chronic inflammation any of the serous membranes may become thickened and milky white, forming a dense and inflexible layer of almost cartilaginous consistence upon the surface of the membrane. In many instances this occurs on the visceral surface of an organ and produces irregular, thick, white plaques. In the case of the heart these

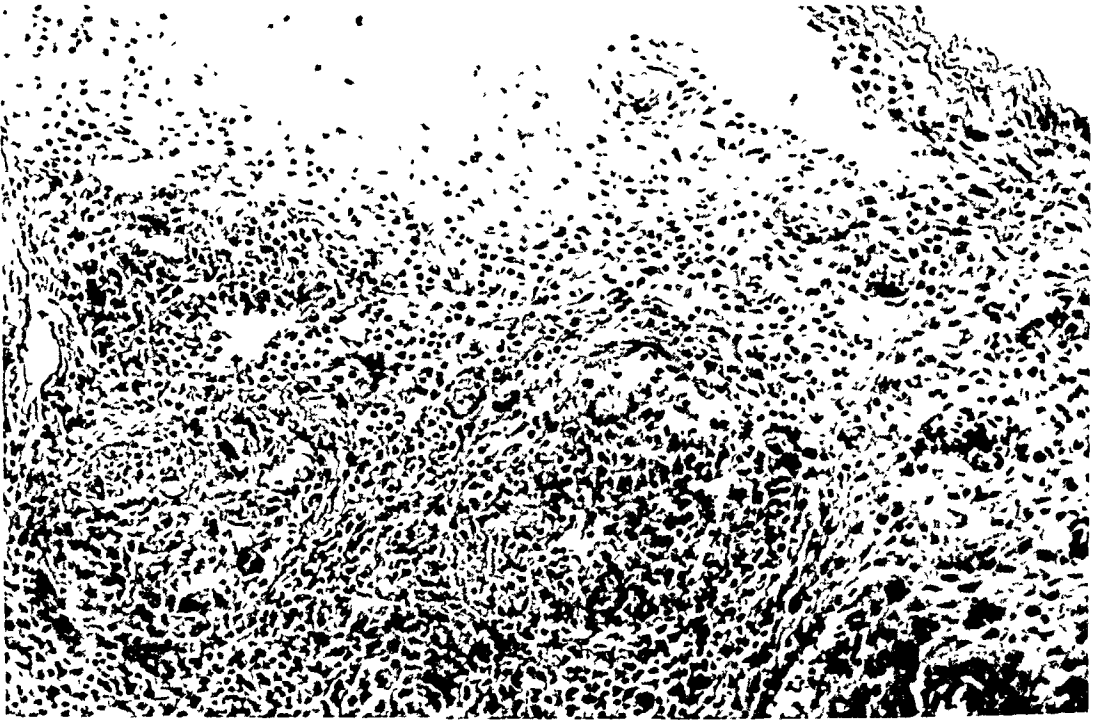
the double o in "foot" or the u in "pull"). The process is of no surgical importance, but it should be recognized when it is encountered in laprotomies. Calcification of such patches is not unusual.

INFECTIOUS GRANULOMA *Tuberculosis* Tuberculosis often affects the serous membranes in the form of tuberculous pleuritis, pericarditis, and peritonitis, and as tuberculous arthritis. In the pleura it is associated with fibrosis and usually with extensive caseation and tuberculous empyema. In the peritoneum it is less apt to occasion thick fibrinous and fibrous inflammatory reactions, but it excites a serous exudate which is very apt to be bloody. The peritoneum is found to be covered with miliary tubercles like small translucent beads. It

may be primary as part of a miliary tuberculosis, or it may represent a spread from a tuberculous lesion of the intestinal tract or fallopian tubes.

Tuberculous pericarditis, on the other hand, excites a massive fibrinous exudate that is shaggy and looks as though it had been "whipped up" with a beater, as it indeed has when we consider the fact that

fibrinous exudate that it provokes, small bodies are produced by the rolling up of masses of fibrin; these may become organized and attached to the synovial membrane or they may float free in the cavity of the joint, much like the "joint mice" described on page 90. They are smaller than the joint mice, however, resembling grains of polished rice or melon seeds; hence



Synovial membrane from joint affected by tuberculous arthritis. There are two well-defined tubercles at bottom of picture.

during its production the heart has been steadily beating. Here the tubercles are usually conglomerate and may produce caseous foci that penetrate into the cardiac muscle a short distance.

Occasionally the process may be exclusively fibrous, as are so many of the tuberculous variety, and may lead to symptoms of adhesive fibrous pericarditis. In this case, the pericardium becomes fibrous and thickened and differs little from that already described in the case of chronic fibrous pericarditis excepting that it shows numerous tuberculous lesions of a specific type.

In the joints tuberculosis takes on the form of scattered tubercles of some size, together with a diffuse inflammation of the synovial membranes and sac. Owing to the

they are often called "rice bodies." They are fairly pathognomonic of tuberculous infection, although occasionally they may be found in other arthritides. With the tuberculous infection there is a concomitant overgrowth of the synovial villi which may reach such proportions as to lend to the surface a very shaggy or furred appearance. Usually there is also considerable pus present.

Tuberculous infection of the synovial sheaths of tendons takes a very similar course and has a correspondingly similar appearance, even to the production of rice bodies, which occur in even greater numbers, as the motion of the tendons in the sheaths tend to roll up a lot of fibrin. This gives a tendon sheath infected with this

disease a peculiar feeling similar to that obtained on palpation of a pincushion stuffed with rice

Syphilis This does not affect the serous membranes as a rule, but it does involve those of the joints in the case of the so called "Charcot's joint," which is secondary to a neurotrophic process incidental to tabes dorsalis. In this disease the synovial membrane, together with the other elements of the joint, become involved in a degenerative process in which the capsule becomes very lax, the synovial membrane fibrotic and eroded, and the bony members involved in the general destruction which leaves the cavity of the joint dilated and filled with cloudy fluid. The process is not dissimilar to that seen in osteo arthritis, but it is painless.

Lycopodium Peritonitis Sometimes the peritoneum may become studded with small tubercles that will be discovered by the surgeon upon reoperating upon a patient who has had a laparotomy at some antecedent date, curious concerning them, he will excise one or two for diagnosis. When the surgical pathologist examines these translucent and pearly tubercles he will be puzzled as to their nature until he makes microscopic sections. In these they prove to be typical foreign body tubercles with epithelioid and giant cells, but the latter contain the unmistakable burr-like spores of *Lycopodium* instead of tubercle bacilli. The source of these spores is a small admixture of lycopodium powder that is added to the talcum powder to make it lighter for use on rubber operating gloves. The lesions are comparatively unimportant, but they should be more generally familiar to surgical pathologists than they are.

Bursitis and "Ganglia" Associated with various types of tenosynovitis are inflammatory conditions of the bursae and tendon sheaths. These are usually very painful and intractable and may necessitate surgical removal.

Bursitis This may be acute or chronic. In the acute form the bursal sac may be

come filled with purulent exudate, or the process may remain serous. The chronic forms are often encountered in patients with a tendency to rheumatoid affections, or they may be the site of specific infectious granuloma, such as tuberculosis. A simple, persisting chronic inflammation usually results in marked fibrosis of the sac, disten-



Subacute prepatellar bursitis. Note layer of old, compacted fibrin on inner surface of fibrous sac (top)

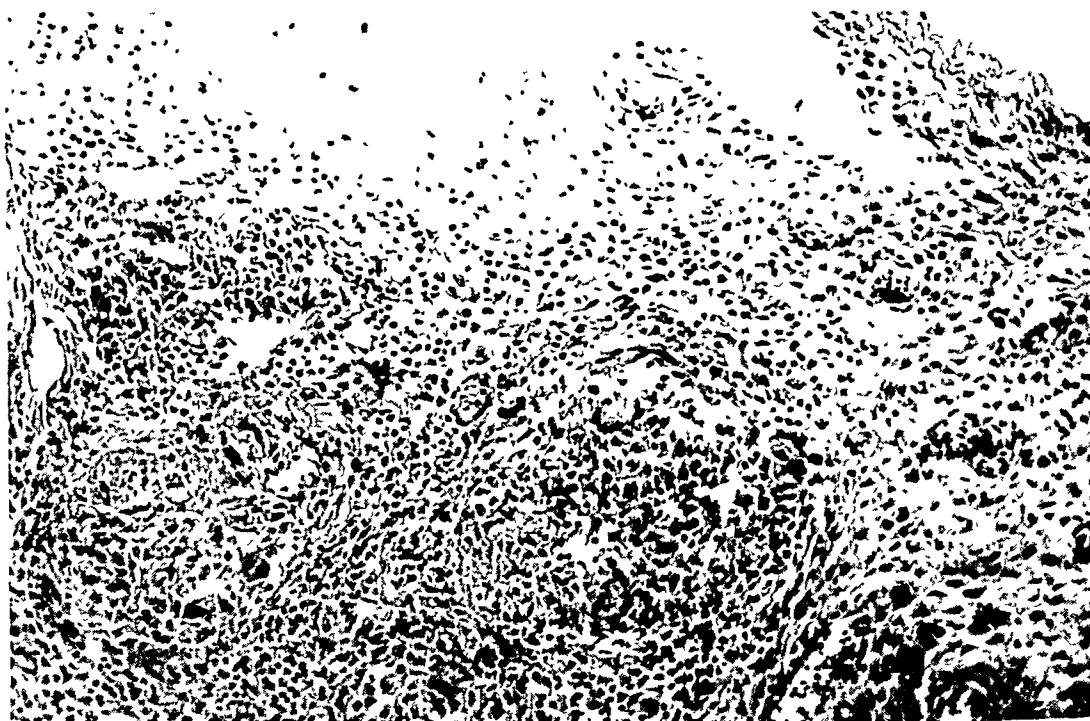
tion of its cavity with fluid and, in the end, calcification. In the last case the bursa becomes filled with material like cream cheese, which is a puree of calcific granules and serous fluid. As this persists, it may become solidified into actually chalky deposits.

Ganglia Almost everyone is familiar with the "weeping sinew" or ganglion of tenosynovitis. As a result of hard usage of a joint, particularly in the course of spading or other manual labor that entails much pronation and supination of the wrist joint, a small sac develops over the tendon of one or another extensor muscle. It is hard and

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necropsy fails to reveal any primary site other than the omentum itself

Ewing describes a fairly wide variety of subtypes of this tumor and remarks that "the proper classification of endothelioma of the pleura and peritoneum still remains a somewhat fruitless matter of discussion" However, he does not consider the derivation of these growths from the mesothelium,

sufficient similarity to those just described in connection with the pleura and peritoneum to exhibit evidence of relationship

TUMORS OF TENDON SHEATH The commonest of these, the giant celled tumor of tendon sheath, used to be known as a "xanthosarcoma" on account of its yellow color and its occasionally malignant appearance under the microscope It is most



Heavy proliferation of mesothelium in very vascular and papillary synovial membrane This might be either an extreme grade of villous synovitis or an early form of synovioma

and if one bears that in mind the matter is less complicated

Synovial Mesothelioma (Synovioma) L W Smith, in 1927, was the first American to report these tumors as such They occur in either sex, usually in younger people, most frequently in the knee, ankle, metatarsal joints, elbow, or shoulder They are predominantly malignant and constitute imperfectly circumscribed growths of varying consistence that are connected with joints or the sheaths of tendons Composed of cells of a great variety of appearance, their most striking feature is their resemblance to carcinoma They exhibit a more or less papillary form of growth, reminiscent of that of the synovial villi When they form cysts these may or may not contain mucoid material On the whole they bear

usually encountered on the fingers, where it arises from the extensor tendons and is therefore quite superficial, usually it is removed with an ellipse of skin overlying it It may be found also on other tendons Grossly it usually is measurable in millimeters, its commonest diameter being in the neighborhood of 8 to 10 mm If allowed to grow, however, it may attain twice that size It is noticed early and seldom has an opportunity to become very large

Under the microscope it is definitely a giant celled tumor, scarcely to be distinguished from those of bone in some instances It is apparently closely related to the group of osseous giant celled tumors, and Geschickter and Copeland believe it to be derived from abortive sesamoid bones in the tendons It exhibits a variable num

may be mistaken for an exostosis. Such ganglia either are dispersed by a sharp rap with a book or other flat implement or are dissected out in their entirety by the surgeon. Pathologically speaking, they are not very interesting, showing merely a cyst with a fibrous wall that may be more or less chronically inflamed and may contain some fibrin as well as the limpid, glairy synovial fluid that is more usual. Occasionally they may be the seat of tuberculous inflammation. They may be found over any tendon.

Tumors of Serous Membranes. The neoplasms of the more extensive serous membranes like the pleura and peritoneum comprise many malignant tumors, because these metastasize to those membranes; rarely they may involve the pericardium. They are scarcely probable in synovial membranes. It is because of the commonness of pleural and peritoneal metastasis that the examination of sediments from the fluid secretions of these affords such valuable data in the diagnosing of generalized metastasis of malignant tumors. Nonmalignant growths of the ovary, the pseudomucinous cystadenomas, may burst and flood the peritoneum with explants which grow exactly like the metastases of malignant tumors and may create surgical problems as to their eradication. These pseudomyxomas of the peritoneum may be simulated by masses of true mucus from appendiceal mucocele, but the latter is usually confined to the vicinity of the appendix and cecum. In the pleural cavity any malignant tumor may break through from the lung and seed itself out over the pleural surface; bronchiogenic carcinomas frequently do so. Intestinal carcinomas occasionally penetrate to the serous surface, pile up, and break off; the detached bits then gravitate to the pelvic cul-de-sacs, where they grow as explants. One may scoop up flaky masses of carcinoma from the bottom of the pouch of Douglas, for instance.

PRIMARY TUMORS. These are usually malignant.

Pleural Mesothelioma (Endothelioma). This is a decidedly rare tumor that requires very careful documentation before the diagnosis can be made with any definiteness. It occurs in middle life in either sex and usually gives symptoms that are so vague and so much like those of a pleuritis that it is seldom recognized until it is too late to do much about it. Its gross appearance is quite indistinctive; it is a tumor that occurs near the pleural surface and spreads over it, and, so far as the surgeon or pathologist is concerned, it might represent a metastatic growth of some sort. On microscopic examination it has a mixed glandular and papillary appearance and presents an unusually bulky fibrous stroma. The cells forming the glandular complexes and covering the papillae are small and cuboidal. Statements that they are "large and lie in nests" usually mean that there has been a mistake in diagnosis and that a bronchiogenic carcinoma has broken out onto the pleural surface. Borst has reported a pleural endothelioma that resembled an epidermoid carcinoma; the present author once examined one of this sort, forming epithelial pearls and acanthomatous masses. In neither of these was there evidence of eruption from deeper in the lung, and yet one doubts that such tumors are truly mesothelial.

Peritoneal Mesothelioma. This tumor is very similar to that just described and it may simulate carcinoma very closely, from both the gross and microscopic viewpoints. It is usually spread out over the omentum, which it puckers into hard masses; careful search fails to locate a primary malignant neoplasm from which this tumor might have metastasized. Microscopically it may present large polygonal cells arranged in disorderly acinar groups, or it may be very much like the pleural variety and exhibit an almost identical picture of small cuboidal cells in adenoid or tubular complexes, sometimes with papillary outgrowths. After dealing with one of these tumors one is always relieved when

Cardiovascular System



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VEINS

VARICOSE VEINS

PHLEBITIS

BLOOD THROMBOSIS

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TUMORS OF BLOOD VESSELS AND LYMPHATICS

GLOSSARY OF TYPES

TREATMENT AND PROGNOSIS

Surgery of the heart has not yet attained a point where it is a pertinent subject for surgicopathologic discussion, although surgical operations upon that organ are becoming increasingly frequent. Likewise, tumors rarely invade the heart and those that arise there primarily are so seldom observed that there are not many to be found in the literature. Rhabdomyomas and rhabdomyosarcomas of cardiac muscle, myxomas and lipomas are occasionally met with in the vicinity of the valves, naturally they cannot be removed surgically.

PERICARDIUM

The pericardium, however, is accessible and is sometimes operated upon for conditions like constrictive pericarditis, sediments from tapped pericardial effusions are occasionally sent to the surgicopathologic laboratory for determination of their cellular content if any. The surgical pathology of the pericardial sac is discussed in the section on diseases of the serous membranes, so further discussion thereof will be omitted here.

Neoplasms of Pericardium Tumors rarely metastasize to this sac, although the malignant group of thymomas may invade it massively by direct extension, and car-

cinomas are very occasionally found there, particularly those which have already reached the mediastinum from some distant organ or from the less distant breast.

ARTERIES

That arteries should be handled very frequently by the surgeon goes without saying, but their diseases rarely present surgical problems that involve the arteries themselves, rather they have to do with the circulatory disturbances in areas supplied by these vessels. For this reason the surgical pathologist has little contact with material from the cardiovascular system. His material consists of yards of varicose veins, which will be discussed later, of amputated extremities, the arteries of which are to be examined for lesions in order to confirm surgical diagnosis, and, lastly, of rather numerous biopsies of skin, muscle, and organs in which the vessels in general are to be examined. The last come chiefly from the medical service of the hospital, where a diagnosis of some vascular lesion has been made tentatively and the physician is in search of confirmation or disproof of his theories. More of this later.

Congenital malformations and degenerative changes in arteries are of relatively

ber of giant cells, seldom as great as that seen in the bony giant-celled tumors. These may lie in spaces in a dense mass of connective tissue that forms trabecular partitions in the tumor. Or the cells may be scattered throughout a mass of plump fusiform fibroblasts that may give evidence of fairly rapid growth and exhibit mitotic figures. Some of the tumors exhibit nests of foam cells or Touton cells; the more of these that are present, the yellower will be the color of the neoplasm. The giant cells may contain brownish pigment which is often hemosiderin and usually accompanies areas of hemorrhage. Other giant-celled tumors may also show this pigment. The fact that the small cells of the matrix of some of the growths are plump and apparently growing actively sometimes lends this tumor the sarcomatous appearance that led to its being called "xanthosarcoma." A beginner in practical pathology knows that the tumor is reputedly noncancerous, but when confronted with this picture he hesitates to give a good prognosis and experiences considerable worry concerning the future of the patient. A few such experiences, however, prove that in spite of its occasionally malignant appearance the growth is not a malignant one.

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the site of the lesion. Thus the entire wall becomes involved in the acute inflammation, and the resulting condition is essentially a segmental panarteritis. As the process subsides there is production of fibrous tissue and scars at the site of the perivascular nodules.

TEMPORAL ARTERITIS This disease differs from polyarteritis nodosa in that it affects the temporal artery and its branches, not

who noted it chiefly in farmers or in women who lived on farms. In 1932 they had collected nine cases, since then many more have been recognized.

Microscopically the lesion is supposed to begin as a small focus of periarteritis, with circumscribed areas of lymphocytic exudate in the adventitia and along the vasa vasorum into the media, which may undergo complete necrosis with extensive hemor-



Small arteriole in areolar subcutaneous tissue showing pronounced panarteritis, a surrounding nodule that is partly edema and partly cellular exudate. The lesion is typical of polyarteritis nodosa.

the smaller arteries, it is not a progressive and possibly fatal disease, the patients are usually elderly and not young, both sexes being equally affected so far as the study of the disease has progressed. The nodules are found to be composed of lymphocytes, plasma cells, and foreign body giant cells, rather than of polymorphonuclear leukocytes, while eosinophils are not found. There are headache and fever, and the patients develop painful nodular swelling of the temporal artery, while the scalp also exhibits tender points which probably correspond to the artery's branches. The disease tends to regress spontaneously, leaving a fibrosed area behind at the site of the lesion. It may be attributable to a senile degeneration, possibly of the vasa vasorum. It was first described by Horton and Magath of the Mayo Clinic

who noted it chiefly in farmers or in women who lived on farms. In 1932 they had collected nine cases, since then many more have been recognized. Thus the picture in a measure resembles that of polyarteritis in its distribution, but the component cells are lymphocytes and their derivatives, and giant cells, which are not seen in polyarteritis. While there may be aneurysmal sacs in diffuse periarteritis and polyarteritis nodosa, none are formed in this disease. The thrombosis that is seen in those affections, however, is present here, and the artery may become a thickened, pulseless cord.

Under certain conditions the temporal artery may also be affected by rather wide spread panarteritis, this is to be kept separate from the type of inflammation just described. It is probably a part of polyarteritis, as it shows involvement of all the coats, with a profuse exudate of polymorphonuclears, both neutrophil and eosinophil, no giant cells are present in such instances.

little importance in surgical pathology; the surgery of the patent ductus arteriosus of Botallo between the pulmonary artery and the aorta is of a reparative type that produces no material for examination, and operations are not performed upon sclerotic arteries.

Acute Inflammation. ACUTE PERIARTERITIS. This is chiefly of importance in connection with the production of mycotic aneurysms, which may develop in many arteries in the body, one after another becoming involved until several aneurysms are present at the same time in different stages of development. They are attributable to infection by micro-organisms, usually of the pyogenic type and not particularly specific. Certain strains of streptococcus, for example, may bring this about in patients who appear to lack resistance.

Inflammation of the wall of the artery leads to thrombosis of its vasa vasorum, and this leads to medial necrosis which weakens the wall and permits it to expand into a saccular or fusiform dilatation, usually the former. The tissue surrounding this becomes infected and inflamed and may break down into abscesses so that the entire structure "blows out" and floods the part with extravasated blood. If this occurs in a situation where the blood may escape into a body cavity or to the surface of the body, fatal hemorrhage readily results. Repeated operations and excision of the accessible aneurysms may keep abreast of the process for a while, but it is usual to have the patient die from hemorrhage or from septicemia secondary to the gangrenous foci surrounding the aneurysms. Small lesions may heal spontaneously with the formation of scars, but the larger ones usually interfere with the circulation to such an extent that the resulting gangrene becomes so extensive and severe as to require very drastic methods of treatment.

When one of these noisome aneurysms is excised and examined one finds a necrotic media and small abscess-like foci of acute inflammation that surround the vasa vaso-

rum and involve them. The picture is one of intense acute inflammation similar to that of the gangrenous appendix. The lesion centers about and is most acute in the region of the media.

POLYARTERITIS NODOSA. This condition was formerly known as "periarteritis nodosa" on account of the fact that it produces periarterial, nodular lesions of an acute inflammatory type. As it has been investigated, however, it evolves as a disease of the media of the small arteries, many of which are compromised. This spreads in both directions until a panarteritis with thrombosis of the vessel results. It is true that at any stage in its development after its inception the resulting nodules may be felt along the course of the arteries, and the lesions are therefore nodose. Young males are said to be more affected than females, although authorities differ on this. If a patient shows such nodules along the course of easily palpated vessels (nodules that are painful and associated with slight generalized symptoms of a rather vague type) the physician often takes biopsies of skin and muscle for microscopic examination by the pathologist, who may find in them typically inflamed vessels. The disease is said by some to be dependent upon allergic or hyperergic conditions, and its microscopic appearance bears this out, although the discovery of small pinkish-yellow nodules that are closely applied to the outer wall of the arteries is demonstrable only on autopsied subjects.

The microscopic picture is reasonably characteristic. There are abscess-like collections of polymorphonuclear leukocytes just outside of the arterial walls, which are often invaded by them; there may be numerous eosinophils present, pointing to allergic response. The media is supposedly the initial focus of the disease, which begins as a degeneration and necrosis of that layer and spreads in both directions, producing the external nodules and affecting the intima so that thrombi are formed at

venules appear to be much affected sometimes they show the sole lesion. There are sleeves of lymphocytes about the arterioles and venules of the derma and about those in the muscle. The arterioles should show masses of deeply eosinophilic material with in their walls, in Masson stains this is red, like fibrin in the green background of the thickened, fibrous walls. It may be very striking in the lymphoid organs, some investigators believe it to be pathognomonic of this disease.

DERMATOMYOSITIS The dermal lesions in this are rather vague, there are patches of discoloration that may resemble urticaria, purpura or erythema nodosum. (The muscular lesions will be discussed in the section on muscle.) The disease affects young males rather oftener than females. The underlying lesions are found about vessels. Under the microscope the dermal lesion is not very characteristic, there is increased pigmentation, atrophy, and the development of vacuoles in the basal layer. The arterioles of the derma are surrounded by an exudate of lymphocytes, indicating a form of periarteritis. In the muscles, which show marked degeneration and necrosis, the vessels are found to be surrounded by similar and rather more copious collections of lymphocytes, while the necrotizing lesions in the walls of the vessels are not particularly characteristic. *More work must be done on the subject, directed toward ascertaining the nature of the vascular lesions which appear to underlie the more flamboyant changes in the structures which they serve.*

SCLERODERMA Here there seems to be a general increase in fibrous tissue in certain parts of the body, with the skin and the alimentary tract—particularly the esophagus—being affected. In the skin there develop areas of pallor, succeeded by thickening and fibrosis. Microscopically one finds what might be termed a "fibrous perivasculitis," the vessels being surrounded by ever increasing masses of fibrous tissue that extends from them into the surrounding tissue, as time goes on, and produces diffuse

necrosis there. Here, again, the lesions appear to center in the vessels, with arteries and veins sharing almost alike in the process. There is some evidence that fibrinoid changes may occur in the walls of these.

As in polyarteritis nodosa, there are hints that all these diseases of small vessels may depend upon some sort of allergic phenomenon, affecting the media of small vessels and through them the regions that they serve.

Specific Inflammation of Arteries

Tuberculous infection of arteries is of importance in the early lesions of pulmonary tuberculosis, but it plays a very minor role in surgical pathology. Syphilitic mesarteritis, which is of great importance in general pathology, is also "out of bounds" in this book. It is the lesions of the smaller vessels that are of importance to us, as they often play a decisive part in aiding one to diagnose biopsies of dermal lesions or other syphilitic manifestations. These small vessels exhibit a perivascular exudate of lymphocytes and marked swelling and proliferation of their lining endothelium, sometimes they may show a frank and rather florid acute panarteritis, with polymorphonuclear leucocytes strewn throughout their walls. Larger vessels demonstrate that the lesions begin about the vasa vasorum and thus involve the media. Any biopsy that presents lesions in the vessels which correspond with this description usually indicates the advisability of a Wassermann test, serology will then prove or disprove that which surgical pathology could do no more than suspect. A diagnosis of lues is always one that has serious potentialities for the patient, so that one should always be very conservative in rendering it unless the signs are very strongly in its favor. The Wassermann test protects the reputation of the pathologist and the patient alike.

Aneurysms Aneurysms are so largely of syphilitic origin that we had best discuss them while we are on the subject of that disease. Anything that tends to weaken the wall of an artery by affecting any of its

THROMBO-ANGIITIS OBLITERANS. Like the forms just described, this has an acute initial stage that goes over into a sclerotic one in time; it is also segmental, inasmuch as it affects certain segments of a given vessel, with considerable lengths of normal vessel interposed. It is a disease in which fully one-half of the patients are Jewish; of these Polish Jews are supposed to represent a large percentage. At first it was called "Jew's disease" or "hebräische Krankheit," but it has been found that this is a misnomer. It was first described by Winiwarter many years ago, but Buerger's investigations in the first decade of this century were so much more thorough that the disease more often goes under his name.

In thrombo-angiitis obliterans there is thrombosis of large vessels with a good deal of acute inflammation in the walls near the thrombus and often a similar involvement of the accompanying veins. Whatever the cause, the intima becomes swollen and a thrombus forms, with time it undergoes organization and canalization, and the vascular wall becomes fibrotic in its vicinity. It is a disease in which lesions may be found in various stages in different vessels at the same time. As a result of the narrowing of arterial channels there may be gangrene of extremities.

It has been noted that thrombo-angiitis and polycythemia vera may occur together, and examination of biopsies of bone marrow in such cases will sometimes show thickening and even acute inflammatory lesions in the capillaries of that organ. In veins the picture is essentially the same as that just described in the case of arteries.

Fibrinoid Necrosis of Arterioles (Necrotizing Arteriolitis). This lesion is more or less prominent in a group of diseases that belong to the already-mentioned loose category of "arterial diseases." These have been familiar to dermatologists for a long time, as they produced characteristic dermal lesions, but it has only recently been recognized that they all appear to rest upon the same vascular basis. They are character-

ized by pathologic changes in the arterioles and smaller arteries and sometimes in the veins as well.

It should be explained that "fibrinoid necrosis" means a necrosis in which a substance resembling fibrin in its staining reactions, but not definitely identified with that material, is deposited in the form of sheets within the vascular wall. These are of uneven thickness and may present nodular thickenings. They stain brilliantly with the ponceau and orange G of the Masson stain, just as does fibrin. Apparently they represent a transformation of the normal collagen or a replacement of collagen that has been destroyed.

LUPUS ERYTHEMATOSUS DISSEMINATUS (ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS). The incidence of this is four times as great among women as among men. Its typical "butterfly lesion," involving the bridge of the nose and the cheeks, is similar enough to that of lupus vulgaris to account for the disease's having been called "lupus." It has little in common with the tuberculous lupus vulgaris, however, and the sooner we devise a new name for it the better, as clinicians are apt to shorten the present cumbersome name to "lupus," which is very misleading.

Just within the past decade or so has it become known that lupus erythematosus is only part of a systemic disease that affects the arterioles throughout the body, produces typical lesions in the heart, kidneys, spleen, and lymph nodes, and may result fatally through the development of severe symptoms referable to the valvular lesions in the heart (Libman-Sacks' disease) and the glomerular changes in the kidneys ("wire-loop capillaries").

In the laboratory of surgical pathology one deals with biopsies from the skin and muscles and, on occasion, from the kidneys; now that the lymph nodes have been found to present typical pictures one may expect more material from that source. All of these biopsies will show changes in the vessels in typical cases. In the dermal biopsies the

fatty acids, these soaps become converted to calcium soap, and thus to carbonates and phosphates of calcium

In larger vessels the atheromatous plaques ("atheroma" being taken from a Greek word meaning "meal" or "groats") do not cause obstruction, in the smaller vessels, however, they may largely surround them and, projecting into them, occlude the lumen. Cross section of such an artery reveals an irregular lumen, with one sector of the intima distorted and asymmetric, containing acicular spaces left by the solution of crystals during embedding and showing conspicuous degeneration of its connective tissue. The internal elastic lamina becomes frayed out at either side of the lesion and may be extensively broken up. Atheromatous plaques may become large and prominent and so centrally softened that the cheesy calcium salts may ooze out between the firmer scales of calcium salts on the surface. These scales may thus become loosened and detached and lead to either of two results: the ulcer that is thus produced may provoke thrombosis, or the calcific scale may lodge in a small vessel and cause its occlusion, as well as damage to its area of distribution. Small arteries like the anterior tibial vessel may gradually become narrowed down until they are a third or less of their normal caliber. In this case there may be time and opportunity for collateral circulation to be developed in healthier vessels in the vicinity.

SENILE ARTERIOSCLEROSIS This occurs in the media of peripheral arteries of elderly subjects as a concomitant of advancing years and senility, and it often takes the form of beaded rings that have been likened to the bands on a pressure hose. This is the Monckeberg type of sclerosis, which differs from the atheromatous type in that it affects the media rather than the intima. The intima may often suffer with the media, showing degenerative alteration. The cross section of such an artery shows a uniformly thickened wall, in contradistinction to the lopsided sclerosis of the atheromatous type.

VEINS

These structures differ from arteries in being thinner, having fasciculated muscular walls in which the muscular bundles are loosely interwoven, rather than arranged in definite strata. Many of them possess valvular pockets attached to the intima. These factors, although apparently trivial, cause a good deal of difference in the lesions of veins as compared with those of arteries.



Portion of transverse section of varicose vein. Note that wall is fibrotic and its architecture somewhat distorted. Otherwise the picture is extremely inert and there is little or no evidence of active inflammation. This is typical.

Varicose Veins This plague of cooks, washerwomen, and policemen is possibly attributable to inherent weakness of the venous walls, but very certainly it is influenced by posture. It is found chiefly in the legs, the veins of the rectum, and those of the pampiniform plexus of the spermatic cords. Factors influencing such veins are gravity, central obstruction causing back pressure, straining at stool or during micturition, and violent exertion. The obstructions that occasion back pressure are represented by the gravid uterus, pelvic tumors, cardiac or intrapulmonary lesions, intrahepatic fibrosis such as cirrhosis, and other such obstructive influences.

As a result of this stasis and expansion, the valves of the unsupported superficial

coats will predispose toward aneurysmal dilatation. The most important coat for maintaining the integrity of the arterial caliber is the media, which is the very layer usually attacked by syphilitic inflammation. However, mycotic infections, tuberculosis, thrombo-angiitis, arteriosclerosis, and trauma may all produce weakness in the wall of a vessel. Thus they may bring about aneurysms.

There are various forms of aneurysm: a "true" aneurysm is composed of a dilated, fusiform, sacculated, or otherwise deformed vessel; a "false" aneurysm scarcely merits the name, for it consists of a peri- or paravascular hematoma that follows injury to the vessel which has pumped blood through a wound in its wall into the surrounding soft parts. If this sort of thing happens within the vessel, however, and blood is pumped along the cleavage lines of the media, it will separate media and adventitia and dissect its way long distances along the vascular wall. This is a "dissecting" aneurysm.

Arteriovenous aneurysms often follow stabs or gunshot wounds that establish a communication between a large artery and a neighboring vein. Such an aneurysm is more interesting to the clinician than to the pathologist; it reveals only a small hole through which the vessels intercommunicate, but like its relatives the arteriovenous fistulae (which are developmental defects) it produces anomalies in circulation as well as hypertrophy in the part supplied by its artery. Cardiac hypertrophy is a common result, as the balance between the arterial and venous circulations, at best a delicate one, is completely upset by the presence of one of these "shunts." Surgeons usually operate upon these arteriovenous aneurysms when they are of the mycotic variety and occur in accessible arteries, but relatively seldom on those of the aorta. When aneurysms arise in the popliteal artery, for instance, they are amenable to operation. Under such circumstances the surgical pathologist may be called upon to examine

the tissue removed and establish a diagnosis as to the probable etiology and nature of the aneurysm.

Arteriosclerosis. This is one of the most important of all degenerative diseases, affecting as it does the aorta and great vessels, the coronary arteries of the heart, and the cerebral blood vessels. Surgeons, however, have little to do with it directly, although surgery may be called into play to remove the effects of arteriosclerosis in the form of gangrenous extremities, hematomas under the dura, and like lesions. When a surgeon attempts to circumvent coronary occlusion by establishing a collateral circulation between the pericardial vessels and the cardiac muscle, nothing will be produced in the way of a surgicopathologic specimen. As the surgical pathologist frequently inspects amputated members in order to document the site of obstructing lesions in the vessels, it behooves him to be familiar with arteriosclerosis.

There is a tremendously rich literature on this subject, and the reader may refer to one or two of the articles listed at the end of this chapter which will offer him further references. Within the last year Hueper has published a series of articles on the theories of the etiology of arteriosclerosis; it is a review that confines itself to this part of the subject only and does not discuss the pathology of the lesions of the various types. Faulty metabolism, heredity, alcohol, tobacco, heavy metals in the diet, improper diet, and a host of other factors have been claimed as etiologic factors. It seems to be agreed that the disease begins as a defect of the intimal connective tissue, wherein there is degeneration of the intima, deposition of lipids in its tissue, formation of soft, translucent plaques of fibrous tissue at the site of these lipid deposits, and a final softening of the plaque by continued lipid degeneration.

The nature of the final mechanism by which the lipids are transformed into calcium salts is problematic. Klotz believed that they are a form of soap developed from

fects the snails in some of the rivers (Snails are the intermediate hosts without which the disease cannot be transmitted)

LYMPHATICS

These touch us only in the realm of diagnosis of tumors, as they are seldom the seat of surgical disorders. The excision of long strips of skin and fascia in the Kondoleon operation for elephantiasis might show infestation of the lymphatics by filaria. There is an unusual disease known as "Milroy's disease" in which there is enlargement of extremities from lymphatic stasis. This appears in familial distribution in members of both sexes. There is a brawny and persistent edema of the affected parts. Under the microscope there is marked dilatation of the subcutaneous lymphatics and a peculiar condensation of the collagenous tissue in the pars papillaris of the corium (that part which lies directly beneath the epidermis), so that one will find a band of dense, more or less avascular connective tissue along the undulating base of the epidermis, and just beneath this a very wide meshed subcutaneous tissue and corium in which all the lymphatic channels are engorged with partly coagulated lymph. A similar condition, known as "nonparasitic elephantiasis," may be encountered in temperate countries among young girls at the age of puberty. In this type of disorder there is also a myxomatous change in the corium and subcutaneous tissue that is very striking. Boyd, who has studied this lesion, believes that there is an inflammatory element in its make up, as he noted foci of chronic perivascular exudate and inflammation in microscopic sections.

TUMORS OF BLOOD VESSELS AND LYMPHATICS

Some of the lesions that are called "hemangiomas" are definitely neoplasms, while others may, in some cases, represent congenital anomalies. There has been much useless classification in connection with blood vascular tumors and it is time for

simplification, as nothing is to be gained by insisting upon the use of some of the currently employed terms. Furthermore, different medical specialties have their own terms for these tumors, so that there may be apparent disagreement between the surgeons, dermatologists, and pathologists which is cleared up as soon as one understands what they are connoting, rather than what they are saying.

Angiomas. It is best to consider these growths as angiomas, although one might speak of hemangiomas and lymphangiomas, in both instances the tumor consists of vascular channels, their content being relatively unimportant. One even sees combinations of the two, particularly in nevi, which are congenital angiomas of the skin.

Fundamentally there are two elements to be considered in any angioma: the vascular endothelium and the other elements of the wall of the vessels, and the tissue just outside of this—the adventitia. Either of these elements may predominate, so that some tumors are largely composed of vascular channels and little else, while others reveal little active growth on the part of these channels, the adventitial tissue being the actual site of neoplasia.

Angiomas may affect any part of the vascular system, so that they may develop in capillaries and exhibit a predominantly capillary structure, or they may grow in the course of large vessels and take the form of coiled masses of these, like earth worms in a bait box ("cirsoid aneurysms"). They may arise from small arterioles and have a plexiform arrangement, or from good sized veins that form cavernous sinuses or "cavernae" and thus constitute cavernous angiomas.

When the adventitial cells are chiefly affected, they may form massive sleeves about comparatively insignificant capillary vessels, these sleeves may be loosely knit and comparatively fibrous, they may be largely cellular and composed of epithelioid histiocytes, or they may take on a stellate arrangement of curly fibers and cells. If

veins become inadequate and no longer functional; the deep veins, surrounded by muscles that splint and massage them, do not become varicose. Stasis is apt to produce fibrosis, and the vascular walls become fibrotic, the muscular coat is largely lost, and calcification may take place in the fibrous wall. The surrounding tissue becomes inflamed acutely or subacutely, as the case may be. This is periphlebitis, which may lead to the production of sluggish ulcers of the skin that tax the ingenuity of the surgeon who has to deal with them. At first the skin over the varicosity becomes boggy and discolored; it is swollen and glistening. Soon it gives evidence of inflammation, and there are attacks of focal cellulitis. This is followed by frank sloughing and ulceration. Very copious hemorrhage may take origin from the varicosity beneath the bed of the ulcer. Boyd points out the rarity of a true phlebitis in connection with varicose veins, and this is readily confirmed by examining a series of specimens which are remarkably free from any lesion save the fibrosis just described. Very occasionally one may find small foci of perivascular inflammation about the vasa vasorum.

Phlebitis. Acute inflammation of the veins, almost always associated with extensive thrombosis, is a very dangerous condition on account of the possibility that bits of the thrombus may become detached and constitute emboli. The pulmonary vessels are the most frequent site for the lodgment of such emboli, which may solidly plug a pulmonary artery or may, by their presence alone, bring about widespread vasoconstriction in the pulmonary bed, with sudden death. Acute phlebitis is a very common concomitant of any acute inflammation, and in the course of routine examination of inflamed appendices and gallbladders one is often struck by its prevalence among the small veins. Often such an infection spreads to the larger tributaries, such as those of the portal vein. This finally reaches the portal vein itself and brings about pyle-

phlebitis ("pyle"- "portal"). This is not uncommon in connection with acute intra-abdominal infections that can drain into the portal system. The vein that is thus affected is found to be full, firm, and distended by a thrombus that may be clotted blood, clotted blood and pus, or even almost pure pus. The entire wall in the vicinity of the thrombus is invaded by polymorphonuclear leukocytes and shows classical acute inflammation which may, in time, result in massive necrosis of the venous wall.

CHRONIC PHLEBITIS. Most instances of chronic phlebitis are referable to an antecedent acute process that may or may not be continuing; there is, however, an odd disease known as "progressive thrombosis of the veins" in which an unknown etiology may bring about thrombosis at any point in the venous bed. Gradually a number of thrombi are developed and the walls of the vein undergo fibrosis and atrophy of their musculature in the region of the thrombi.

Bland Thrombosis. This is a condition that has been recognized only recently. The deep veins of the legs may become thrombosed without any particular inflammatory process taking part in the procedure. This affects elderly people who have been confined to bed for some time; it is strongly influenced by the presence in such persons of obesity, stasis of blood in the part, hyperproteinemia, and dehydration. It may occasionally lead to fatal embolism.

Parasitic Diseases. Certain schistosomes inhabit the perirectal and perivesical veins (*Schistosoma hematobium*), where they cause remarkably little damage to the walls of these vessels. As this disease is prevalent in Egypt, South Africa, and the East it is not improbable that it will be brought back by some of our armed forces and that we shall become acquainted with it in our general hospitals. At present it is rare in the United States, being chiefly found in South Africans from certain parts of the Transvaal, where *Sch. hematobium* heavily in-

similar to that of the type just described, but more cellular and more easily recognized as being composed of adventitial elements. This is sometimes called "sclerosing angioma," but it is not properly sclerosing. Orsos has named it "gemmangioma" from the Latin "gemma," meaning "a bud," as he considers the capillary vessels in the tumor a form of capillary sprout similar to

with adventitial epithelioid cells that lie in masses between the capillary channels.

Glomic Tumor This small tumor, which usually develops beneath the fingernails (although on occasion it may be found elsewhere under the skin), causes exquisite pain that is out of all proportion to the size of the growth. The history of the recognition of the origin of the growth is fascinating, as



Field from glomic tumor composed of thick walled arteries and thinner walled venous channels. If this were impregnated with silver one would see nonmyelinated neurofibrils enmeshing muscular elements of tumor.

that seen in normal granulation tissue. These tumors may exhibit considerable variety; they are most puzzling when they are found near the nose, which is one of their favorite sites, according to Orsos. Microscopically they may show cellular overgrowth of the adventitial cells, with or without myxomatous degeneration of their stroma. In the meninges such tumors are by no means rare; they are well described by Cushing and Bailey, who call them "angio endotheliomas." In these the macroscopic picture is similar to that of any angioma, but when they are examined microscopically it is found that instead of containing a fibrous stroma they are packed

with adventitial epithelioid cells that lie in masses between the capillary channels. The neoplasm had been described before 1924, but it was not until then that Masson took up its investigation—an investigation that led not only to the unravelling of the origin of the growth but also to the discovery of the organ in which it developed, one that was hitherto undescribed. Masson noticed the organoid appearance of the tumor; he was studying and concluded that it must proceed from some organ composed of vascular elements. It was only a short time before he demonstrated the presence of neuromyoarterial glomus beneath normal fingernails and elsewhere under the skin.

The neuromyoarterial glomus, or "glo-

an angioma is arterial it may pulsate and emit a bruit on auscultation; if it is venous it will do neither of these things.

Angiomas that are cavernous and full of blood will be red or purple; those that contain lymph will constitute boggy swellings that are the color of the surrounding tissue. Cavernous hemangiomas are very common in the skin, where they form "strawberry marks" or "birth marks"; they may be very extensive and disfiguring, involving an entire cheek, for instance. Naturally, anything as vascular as they are is subject to severe hemorrhage should it be injured. In the internal organs they are most common in the cavernous form that occurs in the liver near its sharp lower anterior border, rather favoring the left lobe; they are one of the chief tumors of the spleen, where they may be larger than that organ itself. They may, of course, develop anywhere in the body, as vessels are ubiquitous.

Microscopically they are composed of vascular channels, some connective-tissue stroma, and a great deal of contained blood or lymph. When irritated they readily become thrombosed, and surgeons take advantage of this to avoid the inevitably bloody and possibly fatal outcome of operative procedures; they resort to irradiation with the x-ray, which tends to injure endothelium and promote thrombosis. Hemangiomas may become deeply pigmented with hemosiderin from the decomposition of hemoglobin from their contained blood.

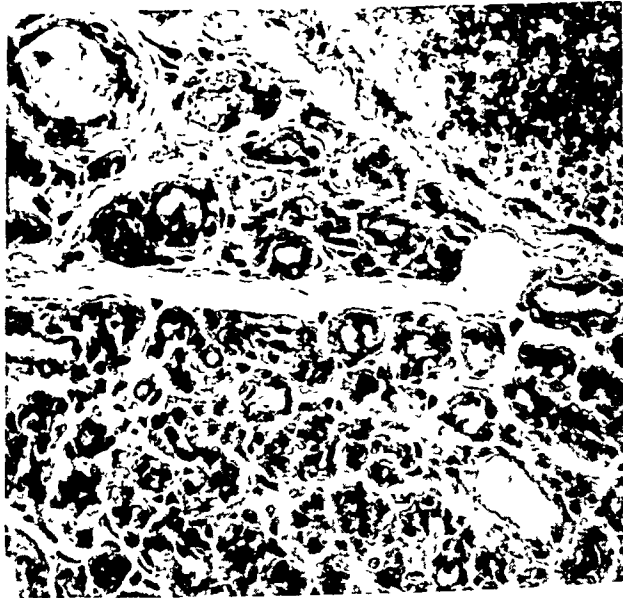
GLOSSARY. For the convenience of the reader the following glossary may be of interest in explaining terms in general use.

Cavernous Angioma. This is an angioma composed of large venous cavernae (much less often arterial) lined with vascular endothelium and containing blood in large quantities. There is a negligible amount of fibrous stroma. Cavernous lymphangiomas are occasionally noted.

Plexiform Angioma. This is one that is composed of vessels narrower than those of the cavernous type and tending to be arranged in a plexiform fashion. They have

walls that are complete in fibrous and adventitial elements, as well as endothelium, thus differing from the following type.

Capillary Angioma. In this form the growth is entirely made up of capillaries that comprise nothing more than vascular endothelium, being composed of practically nothing but capillary channels of endothelium with a minimal amount of supportive stroma.



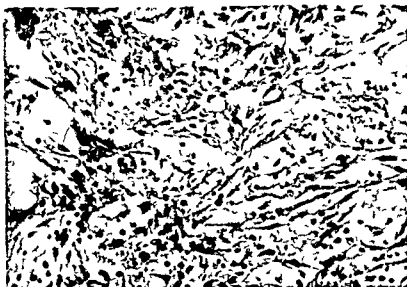
Plexiform hemangioma composed of subarteriolar and arteriolar vessels. Their walls are well formed; there is no metaplasia. Larger vessels supplying the growth with blood are seen at upper corners of field.

Sclerosing Angioma. Angiomas of this type show overgrowth of adventitial elements which produce a great deal of curling fibrillary tissue between rather insignificant and compressed capillary channels. These may be so compressed as to be difficult of demonstration. (See Gross and Wolbach.) The adventitial tissue is arranged in stellate form with a great many vacuolated, sometimes pigmented histiocytes in its meshes. This form of tumor closely resembles the "neuroxanthoma" discussed under neurogenous neoplasms elsewhere in this book. In fact, they may be identical.

Angio-endothelioma (*Gemmangioma*). There is a type of angioma exhibiting a form of adventitial overgrowth somewhat

dom recognizable on gross examination but are readily recognized under the microscope. They take the form of rapidly growing angiomatous tumors composed of immature, "blousy" endothelial cells that may form channels for lymph or blood or may grow in lawless masses containing unlined vascular spaces in which the circulating fluid flows. When one finds unclotted ap

in some circles as "malignant granulation tissue." Such a sarcoma may grow anywhere. If it is in the peritoneal cavity it will constitute masses of gelatinous tissue much like that of a pseudomyxoma—masses that are so insubstantial that they may be scooped out with the gloved hand. This, however, occasions profuse hemorrhage from the myriads of broken capillaries. The



Very malignant form of angioblastic sarcoma known as "malignant granulation tissue" and sometimes "malignant hemangioma." It is composed almost entirely of small capillary sprouts or "gemmæ."

parently circulating blood or lymph in channels that form spaces in an apparently epithelial tumor, one should always suspect that its cells are not epithelial, but endothelial in origin. The vascular spaces of a true carcinoma of epithelial origin are invariably lined by normal endothelium, while those of the angioblastic sarcomas are unlined and naked. Apparently the two main forms just described correspond with the vascular and the adventitial types of angiomas of the nonmalignant group. Occasional angiosarcomas become very pleomorphic, and a diagnosis is always difficult, although one may safely say that the tumor is very malignant.

There is a form of angiosarcoma composed of capillary sprouts so similar to those of granulation tissue that it is known

neoplasm may develop in a tissue or an organ. Orsós considers it to be the malignant form of his hemangioma. Angiosarcoma frequently develops in the meninges, where either the vascular or adventitial cells may play leading or co-stellar roles.

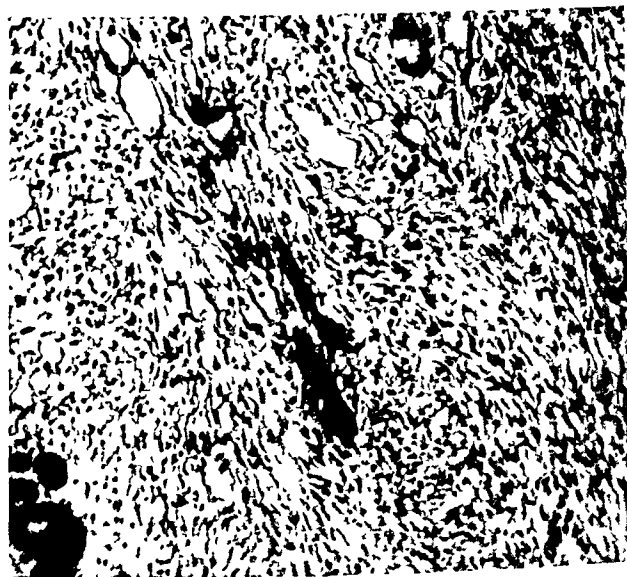
Angioglioma. This tumor has already been discussed under the nervous tissues, but as it also has a very largely vascular element it is mentioned here. There is still some uncertainty as to whether it is composed of vascular and neuroglial tissue, as Roussy and Oberling claim, or whether the apparent neuroglial cells are in reality somewhat disguised adventitial cells. There is always the possibility that they might represent meningocytes, although their pattern of growth seldom follows that of these cells.

mus" for short, is a natural arteriovenous organ that is enveloped in neural filaments that exhibit terminal organelles in the walls of the vessels. The glomus is composed of concentrically arranged veins about small arteries which empty directly into them. Masson and Popoff have described them in detail. The walls of the arterial vessels are very thick and composed of cells modified until they resemble epithelium arranged in several layers, with a somewhat small lumen. The function of the organ is supposed to be connected with the control of body temperature.

From these glomi small tumors develop. As a rule they are measureable in millimeters only and are most inconspicuous. On microscopic examination they are found to be composed of thick-walled vessels resembling those of the arteries in the glomus, but arranged in a most scattered and haphazard manner. Thus far no malignant variety of glomic tumor has been discovered. This growth is readily removed under local anesthesia and does not tend to recur.

Kaposi's Hemorrhagic Sarcoma. One occasionally meets with examples of this elusive disease in which small vascular tumors appear on the skin at various points, grow very rapidly as bluish neoplasms, tend to bleed into their stroma and to produce large ecchymoses, and finally become fibrotic and cicatricial. A patient may exhibit numerous small angiomas that appear and disappear over a considerable period of time. Sometimes he gives a history of having noticed them for years without paying much attention to them, as they tended to "go away" with time. A less favorable outcome is noted in cases where the tumor-like lesions invade the internal organs and end the patient's life by giving rise to copious hemorrhages into the lumen of the alimentary tract or into the peritoneal cavity. The disease remains a completely unknown quantity, without known etiology and very difficult to cope with on account of its elusive character.

Microscopically its lesions resemble poorly developed capillary hemangiomas, with numerous capillary sprouts pushing about in a background of normal tissue which they infiltrate and into which they tend to bleed spontaneously and profusely. This gives the condition its qualifying term "hemorrhagic." With time, connective tissue develops at the site of this capillary



Kaposi's hemorrhagic sarcoma in early stage: a nondescript and definitely malignant-looking lesion producing many young vessels and much immature fibrous tissue; hyaline thrombi in vessels at lower left.

overgrowth and effectually smothers it, producing extensive and very tough fields of fibrous scar tissue; this is known as the "chronic phase" of the disease. In this stage it is extremely difficult to diagnose on a morphologic basis alone; the past history is very important as an aid to reaching a decision. A guarded prognosis is always in order. (We have two patients, however, who have had the disease for years—one for over five, the other for ten or fifteen—without having experienced any dangerous hemorrhages.)

The Hungarian name Kaposi is usually mispronounced in this country; it should be "Káw-po-shee," with the accent on the first syllable, not Kapózy.

Angiosarcoma. There are malignant tumors of the group of angiomas that are sel-

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TREATMENT AND PROGNOSIS. Tumors of the vascular system are always difficult to eradicate; the most nonmalignant type may recur if not thoroughly removed. At our hospital we have always advised wide excision of all growths that show the least suggestion of malignant transformation, with amputation if they arise on an extremity and are outspokenly malignant. In many cases wide excision is the best one can do. Paradoxically, irradiation is of variable importance in the treatment of these tumors: it is not particularly successful in the case of Kaposi's sarcoma, it fails utterly with the lymphangiomas, and it may be of some use in angiosarcomas. This is paradoxical from the theoretic standpoint, as endothelium should be readily injured and susceptible to irradiation, as judged from experimental evidence. The irradiation of large cavernous hemangiomas is frequently resorted to as a curative measure, for it tends to provoke thrombosis of the cavernae, to reduce the size of the tumor by promoting organization, fibrosis, and shrinkage of the growth, and to safeguard the patient against the danger of hemorrhage from the cavernae.

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Bone Marrow

HISTOLOGY

CONGENITAL ANOMALIES

FUNCTIONAL CHANGES

MARROW IN ANEMIA

CHANGES IN MEDULLARY STROMA

INFLAMMATION

TUMORS

METASTATIC

PRIMARY

STROMAL

VASCULAR

MYELOGENOUS

In this and the following chapter we shall consider the pathology of the blood forming organs bone marrow, lymph nodes, and spleen. It would be presumptuous and out of place to include the blood here, as its study is no longer a matter of mere morphology, but includes physics, chemistry, physiologic chemistry, and clinical medicine. It should be understood, however, that blood is a tissue, albeit a fluid and mobile one, that possesses no stroma and consists of an emulsion of cells in a complicated albuminous fluid that contains many elements other than the cells that are suspended in it. The surgical pathologist must understand the morphology of the hemic cells in order that he may recognize deviations from normal and identify these hemic elements when they are present in lesions in the tissues that he is to examine. A diagnosis of lymphogenous leukemia as it is manifested in a section of lymph nodes is placed on a much firmer basis if the pathologist has examined a smear of the patient's blood as well.

HISTOLOGY

One of the most difficult tissues on which to make a pathologic diagnosis is that of the bone marrow. In order to understand its pathology it is necessary that one should have a clear idea of its normal as

pects so as to have a standard from which to work. In early life the marrow is normally very active throughout all the skeletal spaces, but as time goes on this activity becomes limited until during later adult life it is found only in the ribs, the diploe of the skull, the epiphyses of long bones, the sternum, and the vertebrae.

The most accessible site for biopsies of bone marrow is the sternum, from which a button of cancellous bone may readily be removed with a small trepan through an area of local anesthesia. The specimen should be taken deeply enough to penetrate into the cancellous portion of the sternum, as the eburnated outer layer is unfit for examination. The bone should be decalcified and should be stained by the Giemsa or some other variant of the original Romanowsky method. Smears may be made from material obtained by aspiration through a stout needle and may be stained by the Giemsa or the Wright method; they give the same "enlarged" effects as do smears of blood, as the cells flatten out on the glass and the smears are not as comprehensive as the biopsies, which present the marrow as a tissue and not as a mere sample of component elements.

Bone marrow is composed of a framework of loose reticulo endothelium in which are embedded the hematogenic cells

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notic nucleus of a degenerating cell, here, however, the process is known as "trachychromasia," not "pyknosis." Successive stages in the development of the erythrocytes occur as cells in each phase divide mitotically, with the production of an element that almost resembles an erythrocyte but still contains a trachychromatic nucleus and exhibits a reticulated cytoplasm filled with red staining hemoglobin. The extrusion of the nucleus follows, and the cell is then an immature erythrocyte which, on account of its reticulated appearance, is known as a "reticulocyte." With the disappearance of this reticulum, the cell is finished and is a full blown erythrocyte which is non-nucleated and cup shaped and has a thickened and rounded outer rim. It measures about 7μ in diameter in smears.

MYELOCYTES Precursors of the granulocytic leukocytes, these constitute so prominent a part of the marrow as to derive their name therefrom, myelocytes are "marrow cells." These undergo mitotic division to produce replacement myelocytes and, by further differentiation, leukocytes. They possess reniform nuclei with a moderately dense karyoplasm and granular cytoplasm in which the granules may be neutrophilic (taking on an indifferent color in most dyes), eosinophilic, with coarser structure and staining brilliant vermilion, or basophilic, taking on a deep blue or azure color with these stains.

NEUTROPHIL MYELOCYTES *Promyelocytes* These are slightly basophilic, with acidophilic areas that are characteristic and lend the cells a pied appearance. Their nuclei are reniform and contain several nucleoli. Granules are scattered throughout the periphery of their cytoplasm and within the acidophilic spots in a rather haphazard and scanty fashion.

Myelocytes By further maturation myelocytes are produced which show a tendency on the part of their nuclei to become horseshoe shaped and to lose their capacity for mitotic division. The nucleus becomes progressively constricted and divided into

coarser masses of chromatin connected by thread like bands. The horseshoe or "transitional" form thus becomes an "immature" one (so common in inflammatory exudates and in the blood during leukocytosis) which, by a process of further lobulation, goes over into the mature neutrophil polymorphonuclear leukocyte, the "polly" of popular parlance.

Eosinophil Myelocytes These practically recapitulate the changes detailed for the neutrophils, excepting that their granules tend to stain basophilically in the promyelocytic stage, after which they become acidophilic. Eosinophils are normally less numerous than neutrophils in the marrow, but their brilliant vermilion color renders them unduly prominent and easily recognized, which makes them seem more numerous than they really are.

Basophil Myelocytes Comparatively few of these are noted in the bone marrow, probably because of the ready solubility of their granules in water, which indicates the necessity for using an alcoholic fixative when desirous of demonstrating them. Normally these granules are variable in number and mitotic division is not very lively. In the blood stream mature basophils form a small percentage of the total leukocytes (0.5 to 1.0 per cent), but in the tissue they may congregate in considerable numbers, particularly in the dermal lesions of urticaria. Here they are known as "mast cells," from the German *masten*, "to feed for market" (cf. "*Mastochs*"), but the word is a mongrel at best, combining German and English, and it should be discarded. These basophil myelocytes mature into basophil polymorphonuclears in the same fashion as that by which the neutrophil and eosinophil myelocytes produce their mature varieties.

Monocytes The circulating monocyte is supposed by some to originate from hemocytoblasts, but a consensus of opinion attributes its origin to the reticulo endothelium of the marrow. It is also quite likely that many of the monocytes, once their race is established after embryonal life, continue

which are originally derived from this reticulo-endothelium. Besides these there are capacious sinuses lined with reticulo-endothelium and filled with circulating blood and a variable amount of adipose tissue that increases until it completely replaces the other elements in most of the bones of older individuals. The development of "yellow" or adipose marrow from the "red" or active type is very variable; it may be a process of senescence or it may occur in connection with anemia; conversely, when there is need for hemic cells as the patient recovers from anemia, yellow marrow may be reconverted into very active red marrow for a time. After prolonged starvation or wasting disease, the adipose tissue may also undergo exhaustion (as it is a depot of reserve fat) and become converted into a mucoid or gelatinous substance.

Stroma. The stroma has the same general structure as has that of the lymph nodes, with a syncytium of large, undifferentiated reticulo-endothelial cells closely associated with reticular fibers that bind the tissue together. These are a prolific source of macrophages and monocytes. In this framework course thin-walled blood sinuses. The stroma is condensed into a membrane over the inner surface of the bony trabeculae to constitute the endosteum of the bone. Blood vessels that supply the sinuses are in no way peculiar, being much like those of any part of the body; it is their terminal sinuses that exhibit the thin, permeable walls which distinguish them.

Cellular Components. **HEMOCYTOBLAST (MYELOBLASTS).** The "stem cells" from which almost all the cells circulating blood, including the erythrocytes, are derived, are large ameboid elements with a rather homogeneous cytoplasm, large reniform nuclei, and prominent, angular nucleoli; they sometimes exhibit pale cytoplasmic vacuoles. By their division and differentiation of the daughter cells thus produced they are supposed to create all the forms seen in the marrow exclusive of stroma and reticulo-

endothelium. They are grouped in clusters, sometimes forming small islets if hemopoiesis is lively and the need for replacements is acute. The lymphocytic cells of the marrow are supposed by the "dualists" to be derived from these stem cells, while the "monists" believe that they are true lymphocytes and independent of them.

LYMPHOCYTES. Small cells whose appearance is identical with that of the lymphocytes are scattered throughout the meshes of the marrow. They may be lymphocytes which immigrate to this tissue (as indicated by the fact that plasma cells are often found there and may assume formidable numerical proportions in "plasmocytic myeloma") or they may be considered as "micro-myelocytes," allied to the myelocytic cells to be described presently. The choice of theories is an open one; many of us incline toward the former.

Myeloid Elements. **ERYTHROBLASTS** These are spherical cells with spherical nuclei that divide by mitosis and show a variable amount of a yellowish material (hemoglobin) diffusely distributed in their cytoplasm; as the cell matures this becomes increasingly prominent until it fills the entire cytoplasm. The nuclei always show what Maximow and Bloom describe as a "checker-board" distribution of angulated particles of chromatin and nucleoli that gradually tend to dwindle and disappear.

The youngest erythroblasts (pronormoblasts) exhibit a basophilic cytoplasm which fades and becomes rather mixed in its staining reaction as hemoglobin increases, while some of the basophilic matter remains. At the same time acidophilic substances begin to take on a redder color, so that the resulting hue is a mixed violet. The nucleus is relatively pale. This stage is known as the "megaloblast" (basophilic normoblast), as the cells are larger than those that succeed them; they may be called "polychromatophil erythroblasts" or "normoblasts." Following this they become smaller and their hemoglobin more evident; the nucleus is dark and resembles the pyk-

possible, however, that the presence of leukocytes in a leukocytosis due to inflammation brings about capillary permeability in inflamed areas similar to that which the large number of leukocytes normally present in the bone marrow utilize regularly under normal and noninflammatory conditions

A good deal of space has been dedicated to this description at the risk of introducing a lot of normal histology, but it is only through a thorough familiarity with normal standards that one may appreciate the deviations therefrom. The decision as to these deviations is particularly tricky and difficult in the diagnosis of biopsies of bone marrow where there may be delicate shades of difference between normal, hyper-, or hypoactive marrow and tissue that shows definite pathologic lesions

PATHOLOGY

Congenital Anomalies There has been no report of complete aplasia of this organ, although some children exhibit an early involution of the marrow, in which it becomes progressively atrophic and hence aplastic with an increase in its content of fat. This somewhat parallels the normal changes in the marrow seen in subjects that are aging.

Functional Changes The various forms of anemia may be ascribed to two chief causes: either the marrow is not forming blood cells in sufficient numbers or these are being destroyed in the circulating blood at a rate faster than that of normal production by the marrow.

APLASTIC ANEMIA In the former instance one speaks of "aplastic anemia." This may be due to a number of causes that affect the production of hemic cells in various phases of their formation. There may be a failure on their part to mature properly, and one may observe sections in which there are plenty of immature forms which exhibit abundant mitoses, but in spite of this there is a paucity of mature cells. Under such circumstances islands of hemocytoblasts may grow actively, and their cells

may divide as though there were a distinct stimulus to the production of blood cells, but none that would insure the completion of the process by bringing about their full maturation. Very few mature forms will be noted in this case.

A second variety of aplasia takes the form of a complete disappearance of most of the hemic cells from the marrow, certain chemical agents like amidopyrine, benzene, or many of its substitution products, as well as some of the sulfonamides, may bring about this change, in which case the functional cells become replaced by nonfunctioning fat cells. This is aplastic marrow in the strictest sense of the term.

MYELOSIS The marrow may be extensively invaded by certain tumors, notably prostatic and mammary carcinomas, which not only replace the marrow and thus destroy it, but destroy the bone as well, thus giving rise to the presence of certain acid phosphatases in the circulation which provide a clinical clue to the presence of these bony metastases. As a result of this, marrow is produced heterotopically in such organs as the spleen, liver, and lymph nodes—a process known as "myelosis." One may then find all the elements of the marrow, save its adipose tissue, scattered through the splenic pulp, in that of lymph nodes, or in the sinusoids of the liver. Notice is at first attracted to this by the discovery of megakaryocytes which, on account of their large size and distinctive nuclei, immediately claim attention. Further examination will reveal promyelocytes and erythroblasts, with their derivatives, and one may even find islands of hemocytoblasts. The last are particularly evident in the hepatic sinusoids, where they form blood islets. During fetal life the liver normally shares in hemopoiesis, and this persists for a few weeks after birth, when it should gradually disappear. It is not strange, then, that the liver should be capable of once more taking over the function of hemopoiesis if the marrow becomes incapacitated.

to perpetuate themselves by dividing while circulating in the quieter reaches of the blood stream. They have been called "blood-histiocytes" by Aschoff, have been extensively studied by a number of people, including Cunningham, Sabin, and Doane, and have long constituted a bone of contention in histologic and hematologic circles. They are best studied in supravital preparations stained with neutral red and Janus green. The cell is about the size of a lymphoblast (about 10μ in diameter) and has a reniform and rather vesicular nucleus with a small nucleolus (which may be accompanied by one or two large karyosomes). It possesses a relatively large amount of cytoplasm in which there may be vacuoles. In supravital sections and smears, collections of coarse granules may be observed in the "hilum" of the nucleus, clustered into a characteristic rosette. The granules stain brick red with neutral red, navy blue with Nile-blue sulfate, and brown to black when impregnated with silver. It is possible that these cells become larger when they leave the vessels and constitute macrophages.

Megakaryocytes. These large and showy cells are also derived from the hemocytoblasts and are true giant cells and not syncytia; they attain a diameter of 40μ on occasions. In their younger phases they present a simple nucleus like that of the stem cell, but as they develop this becomes irregularly lobulated. It is generally believed that extrusions of pseudopodial extensions from this nucleus through the membrane of the cell, with subsequent detachment of the extracellular projection thus formed, gives origin to the platelets. Other theories as to their production exist. The mitotic habits of the megakaryocytes are somewhat analogous to those of neoplastic giant cells in that after division the daughter nuclei fuse to form a larger one, and this process continues a number of times until the nuclear material thus accumulated is very abundant.

Mechanism of Hemopoiesis. After embryonal life the supply of cells to the blood takes place through the multiplication of the reserve cells already mentioned. As early forms of erythro- and myeloblasts develop they do not all undergo differentiation into adult types; some of them remain undifferentiated and serve as a reserve from which mature cells may be formed at a future time. When that happens some of these new cells will again remain as a reserve supply in the marrow, while the rest will become adult forms. This is known as "homoplastic hemopoiesis." Under conditions of stress, when there is a sudden call for additional cells, the hemocytoblasts may again be called upon to divide and produce new erythroblasts or promyelocytes. When they divide they produce two cells of an identical variety, never one erythroblast and one promyelocyte. Maximow and Bloom call attention to the fact that the newly produced cells then form small islands composed of even numbers of immature cells, indicating that these have been produced in pairs. This is "heteroplastic hemopoiesis."

The factor that determines whether erythroblasts or promyelocytes shall be produced by this type of division of an hemocytoblast remains to be discovered. Under conditions similar to those just mentioned, when there is need for more leukocytes, it is possible that the reticulo-endothelial syncytia of the stroma of the marrow may also respond by resuming their embryonal function as "blood islands" and producing more hemocytoblasts to reinforce those resident in the marrow.

Once formed, the myeloid cells destined to become circulating cells of the blood penetrate the walls of the venous sinuses and are swept away into the blood stream. The endothelium of these sinuses allows their ready passage, whether they are capable of ameboid motion or not; this is a process similar to that observable in the capillaries of an inflamed area, without the factor of inflammation being present. It is

production may depend upon several factors (1) nutritional deficiency, (2) inhibition of the production of cells by such agents as injurious chemicals, and (3) replacement of normal, functioning bone marrow by a tumor which may either be primary in that organ or metastatic from another one. There may be an apparent decrease in the size of the erythron, i.e., an apparent anemia which is caused by an increase in the plasma of the blood such as occurs in connection with nephritis and pregnancy. This is really "diluted blood," not anemic.

The anemias may best be classified on a morphologic basis, which is apparently the most workable one from the standpoint of hematologists and clinicians, who use it very widely. Under this system, the size of the erythrocyte and the concentration of hemoglobin within it are taken into account, so that there may be three main groups on the basis of the size of the red corpuscles alone: macrocytic, normocytic, and microcytic. These terms are self explanatory. The groups may be split further into two subtypes: the hypochromic, which exhibits too little hemoglobin per corpuscle, and the hyperchromic, which exhibits too much. As already stated, it is not intended that we delve too deeply in the niceties of the diseases of the circulating blood, if the reader is interested he may consult such excellent textbooks as those of Wintrobe or Kracke, the former fairly bristling with excellent bibliographies. Let it suffice here that we set down the main characteristics of these dyscrasias with the purpose of correlating them with the pathology of the bone marrow.

MACROCYTIC ANEMIA There are numerous forms of macrocytic anemia, depending upon a variety of etiology. They may be attributed to such causes as lack of the erythrocyte maturing factor of the liver or of the intrinsic factor of the stomach or of the extrinsic factor in food. Thus diseases of the liver will interfere with the production of the factor secreted in that organ,

cirrhosis, for example, will bring about anemia in many instances. If this is the only factor that is interfered with, one is dealing with an "achrestic" anemia which is attributable solely to the lack of this particular factor. In pregnancy the fetus may pre-empt so much of this substance that the mother suffers from a lack of it and becomes anemic. Atrophy of the gastric mucosa will interfere in a like manner with the production of the intrinsic factor. Again an important link in the chain of stimuli to the formation of blood is strained or broken and anemia results—usually an anemia that is so pernicious in its manifestations that it goes by the name of "pernicious anemia." Atrophy of the gastric mucosa, or replacement of that membrane by extensive carcinoma, will produce this loss of the intrinsic factor, as well as a lowering of the hydrochloric acid until it may be absent from the gastric juice. Lack of the extrinsic factor, the third in the group of stimuli to the production of blood cells, may be due to poverty in that factor of the food eaten by the individual, or to an inability on the part of the patient to absorb it when it is present in ample amounts. Thus, diseases that interfere with proper absorption from the alimentary tract will obviously prevent absorption of the extrinsic factor and result in anemia. This is seen in connection with such diseases as sprue, dysentery, and other inflammatory intestinal affections, or with celiac disease in children. Certain parasites, notably the fish tapeworm (*Diphyllobothrium latum*), may also occasion macrocytic anemias.

Marrow in Pernicious Anemia In this most important of macrocytic hyperchromic anemias there are very characteristic changes in the bone marrow which are best noted at the time of relapses that occur in the vacillating course of the disease. There is a well marked hyperplasia of the erythroblastic elements and the production of cells that are peculiar to pernicious anemia and are not seen in other forms of the dyscrasia. These are known as "megaloblasts."

HYPERPLASIA OF MARROW. Hyperplasia of a physiologic type, in response to physiologic or pathologic stimuli, may be simulated by an idiopathic hyperplasia which becomes pathologic and assumes neoplastic proportions. This will be discussed when we come to the tumors of the marrow. The type of hyperplasia noted in polycythemia vera (a dyscrasia characterized by a great increase in the production of erythrocytes until they exceed the normal count by a million cells or more per cubic millimeter) exhibits activity of the erythropoietic elements that is not readily recognized. There is a more evident increase in the number of megakaryocytes, and there are alterations in the walls of the subarteriolar capillaries whereby they become thickened and fibrotic and may sometimes manifest inflammatory changes. In such instances the endothelium is swollen and narrows the lumina, and there is evidence of angiitis of an acute type with leukocytes congregating about the smaller vessels and collecting within the walls of the larger ones, which may be thrombosed. These are exceptional changes, but they point to a relationship between at least some varieties of polycythemia and vascular diseases of the type of thromboangiitis obliterans. That the fibrous thickening of vascular walls in polycythemia might lead to anoxemia which, in turn, might stimulate erythropoiesis is an alluring theory, but one that is not easy to prove conclusively.

A variety of polycythemia which is more in the nature of an erythemia is noted in individuals who live and work at high altitudes, as has been demonstrated by Barcroft and his co-workers in their investigations on workmen in the mines of Cerro de Pasco in the Andes. Such a condition would, of course, be a physiologic response to a relative anoxemia in regions where, because of the great altitude, oxygen is less available on account of its paucity in the rarefied atmosphere. With the changes in the bone marrow in these workmen there was found

to be compensatory emphysema and other similar changes.

Bone Marrow in Anemia. If we are to understand the histology of the marrow in certain forms of anemia we must know something about anemia itself, although the subject lies outside of surgical pathology and in the realm of hematology, where it belongs on account of the fact that its study requires a combination of clinical pathology, chemistry and clinical medicine. To boil the matter down to dimensions compatible with a very brief survey, the following short section will possibly suffice to correlate the pathology of the bone marrow with the characteristic findings in the patients with one or another form of anemia.

The circulating blood and its immature fixed portion in the bone marrow may be considered as a hypothetical organ, the "erythron," which differs from other organs in having most of its volume in a circulating, suspended, and stromaless form. Anemia may be considered as an atrophy of this organ. There is a reduction of erythrocytes to a point below normal limits per cu. mm., a lowering of the hemoglobin that they contain, and a decrease in the volume of packed erythrocytes in the hematocrit. This last is a tube in which blood is centrifugated for a specified period at a specified speed and the resulting packed layer of erythrocytes measured. Theoretical terms are sometimes used to separate certain phenomena in the circulating blood from the anemias; thus, "oligemia" applies to a reduction of the total volume of blood in the body, "oligocythemia" to a decrease in number of erythrocytes, and "oligochromemia" to a lowering of the amount of hemoglobin.

Anemia may be caused by: (1) the loss of blood in connection with hemorrhage; (2) a decreased production of hemocytes by the bone marrow; or (3) a faulty production of these cells. Loss of blood may be acute or chronic, according to whether it follows copious and sudden hemorrhage or a slow and protracted seepage of blood. Hemolysis may destroy it slowly. Decreased

young girls and women and was occasionally noted in boys. Attributable to unsuitable food and poor hygiene, it has been diminishing at such a rate that it is now seldom seen, probably because of improved conditions. It is due to a deficiency in iron and is characterized by this plus a reduction in the number and size of the erythrocytes, all of this is quickly overcome by iron therapy. Too little iron in the food, a low absorption of this from suitable food, and a continued loss of blood from chronic ulcers or other causes are decisive factors, in pregnancy the fetus may utilize so much iron that insufficient amounts are left over for the mother. This form of anemia may also result from hookworm infestation or from sprue or dysentery. The gastric juice is usually hyperacid, but there is a chronic form of the dyscrasia in which achlorhydria may appear.

In this form of anemia the bone marrow is hyperplastic and shows a relative as well as an absolute increase in normoblasts which is in sharp contrast to the paucity of erythrocytes in the circulating blood. Megaloblasts are not observed, the predominant cell being a small, polychromatophilic normoblast which is sometimes called a "megaloblast," particularly by histologists. Granulopoiesis is not interfered with in any way.

Mediterranean or Cooley's Anemia This is a microcytic type of anemia that shows distinct peculiarities. It is seen in members of the nations that dwell along the shores of the Mediterranean in Italy, Greece and other countries. It has a familial incidence and an obscure etiology, children suffering from it show developmental defects in their faces which makes these little patients look enough alike to be brothers and sisters. The circulating blood not only exhibits microcytic erythrocytes but "target cells" as well, these are red cells with small "bull's eyes" at their centers like minute areas of cytoplasmic condensation. The marrow shows marked hyperplasia and contains many hemocytoblasts or "stem cells."

There is also hyperplasia of the myelocytes and megakaryocytes, while the stroma may also become hyperplastic and give rise to numerous phagocytes that contain a brownish pigment and lend to the marrow somewhat the appearance that is noted in Gaucher's disease. The splenic changes may be even more easily confused with that disease, they will be discussed under consideration of the spleen.

Sickle cell anemia In this peculiar disease, which is observed most often in Negroes and mulattoes, the erythrocytes in the circulating blood become sickle shaped or elongated and they also show peculiar fraying out at their margins. The marrow exhibits from 50 to 70 per cent of nucleated red cells that are chiefly normoblasts, a few of these manifest distortion of their outline that presages the marked sickled deformity of the mature erythrocytes that evolve from them. No megaloblasts are seen. Megakaryocytes are increased in number. The leukocytes may show many immature phases, with a definite "shift to the left" in which the nuclei are either band forms or horseshoes, or at best possess few lobules. Wintrobe mentions the presence of peculiar strands of what appears to be erythrocytic cytoplasm that are 2μ in diameter and may extend across a whole oil immersion field.

Changes in Stroma of Bone Marrow These usually affect the adipose tissue and the reticulo-endothelial elements. The former may lose their neutral fat, which is replaced by a mucoid fluid that presents in the form of small droplets in the cachectic cells that have reverted almost to the embryonal "mulberry cells." This in turn gives rise to the mucoid or gelatinous marrow noted in connection with wasting diseases, starvation, and similar processes.

Lipoidoses Lipoid dyscrasias which are poorly understood and affect many parts of the body produce definite pathologic pictures in the bone marrow wherein one finds an increase in the number of phagocytes, which become swollen and vacuolated, the vacuoles containing lipid substances of

Unfortunately there are two types of nomenclature applied to the bone marrow: the histologists refer to the polychromatophilic normoblast as a "megaloblast," while the clinicians reserve this term for the abnormal cells noted in pernicious anemia which were already known by that name when it was applied to normal cells. In this book we shall understand that the *abnormal* element of pernicious anemia is referred to when the term "megaloblast" is used.

These cells are large and have a nucleus with a chromatin network that is very delicate and resembles scrollwork in its appearance. Their cytoplasm may exhibit three types of staining reaction: it may be so basophilic as to mislead one into believing that these cannot be precursors of red corpuscles; it may show a nondescript color reaction or polychromatophilia; or it may be acidophilic and stain so brightly red that there is no difficulty in recognizing the cells' alignment with the erythroblastic elements. These cells usually lie grouped in clumps of from three to seven cells, as though they had been produced in company with one another. Normoblasts, on the other hand, are relatively few by comparison with the megaloblasts. Mitotic figures are not appreciably increased in number.

Not only the red elements of the marrow are affected by the disease; the leukocytes also exhibit atypical forms. One finds gigantic white cells with a diameter of 30μ or more which may represent any stage in the development of the leucocyte but are most frequently seen in the metamyelocytic phase. Their nuclei are proportionately large and may show an increased number of lobules, forms like rings or doughnuts, or other bizarre irregularities. Their cytoplasm is usually light blue and poorly developed when studied in smears stained by Wright's method. Besides these changes, it is noted that reticulum cells and lymphocytes are increased in number. Thus the bone marrow presents a very typical picture in pernicious anemia. In other forms of macrocytic anemia there are few distin-

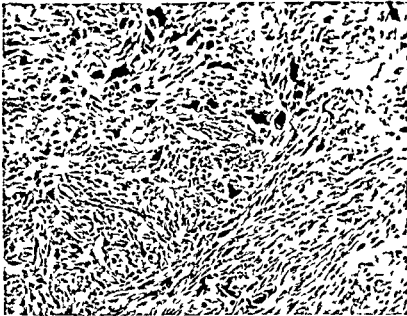
guishing features and a biopsy is of value in a negative way, as it rules out the presence of pernicious anemia, without giving any clue as to the type of macrocytic anemia with which one is concerned.

NORMOCYTIC ANEMIA. In this the erythrocytes are neither large nor small. The disease is divisible into three groups: (1) that which follows hemolysis; (2) that which is due to severe hemorrhage; and (3) that which is attributable to aplasia of the bone marrow. The last of these has already been discussed in connection with aplastic bone marrow. The hemolytic type may be observed in the familial congenital hemolytic jaundice and in connection with chemicals that cause hemolysis or with diseases that do the same. In hemolytic jaundice there is marked erythropoiesis of the normoblastic type, in which these cells constitute from 25 to 60 per cent of all the nucleated elements. Megaloblasts are not seen. In anemias due to severe hemorrhage one finds a marrow that is doing its best to keep up with the loss of hemic cells from the circulation, but as this is quasiphysiologic one finds very little of a distinctive nature. The circulating blood may show a transient macrocytic phase with the additional feature of many reticulated cells which are thrown out before they are mature as a result of the marrow's overactivity.

MICROCYTIC ANEMIA. There is a simple type of microcytic anemia which is neither hypo- nor hyperchromic, but this is a poorly defined group that is associated with subacute and chronic diseases and brings about no characteristic changes in the bone marrow.

HYPOCHROMIC MICROCYTIC ANEMIA. The hypochromic form of microcytic anemia exhibits several subgroups, some of which are accompanied by very characteristic pathologic changes in the marrow and other organs.

Chlorosis. The first of these used to be known as "chlorosis" and was a form quite familiar to physicians in the early part of the present century. It was very common in



Malignant giant celled tumor of bone, probably arising from retothelial tissue in marrow. It has little resemblance to ordinary giant celled tumor, but rather closely simulates osteolytic osteosarcoma.

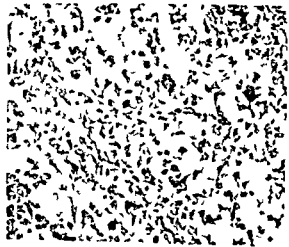
metastasize to the bony skeleton, where they invade the marrow, in which they arise via the circulation.

PRIMARY TUMORS As the marrow is composed of stroma, vessels, hemopoietic tissue and adipose tissue, any of these may constitute the site of primary neoplasia.

STROMAL TUMORS The reticulo endothelium seldom gives rise to nonmalignant tumors unless the giant cell tumors of bone may be considered as such, but malignant varieties are not uncommon.

Reticulum celled Sarcoma There is a certain amount of evidence to show that many of the central sarcomas of bone, the so called "osteolytic sarcomas," may belong to this category. Ewing is not very definite in separating them from one another and tends to group the "endotheliomas" together. Grossly noted, these tumors grow in the marrow cavity until the bone overlying them is thinned out into a veritable egg shell and, on palpation, gives the typical "egg shell crackle." The growths are very hemorrhagic, and where they are not dark red they are yellowish, like marrow. On microscopic examination they are seen to

be composed of anastomotic cells that are, in the main, small and stellate but may show from a few to many gigantic forms with lobulated nuclei that are hyperchromatic and often very bizarre. These large cells will show atypical forms of mitotic figures, the Y mitosis being a favorite among them.



Rethothelial (reticulo endothelial) sarcoma of bone. Among the fairly well differentiated and anastomotic cells there are occasional neoplastic giant cells.

varied nature. In Gaucher's disease the spleen is flooded with enormous phagocytes that are shaped like melon seeds and contain a delicate meshwork of cytoplasm enclosing somewhat elongated vacuoles filled with a cerebroside called "cerasin." In Niemann-Pick's disease these cells are more like foam cells or fat phagocytes and contain sphingomyelin, while in Hand-Schüller-Christian's syndrome similar cells are found which have taken up cholesterol esters. Later on we shall discuss these more in detail in connection with the spleen. These infiltrations, in sharp contrast with the invasive metastatic tumors already mentioned, do not seem to interfere materially with the marrow's hemopoietic activity.

MYELOFIBROSIS. There is a strange and rarely seen condition known as "myelofibrosis" in which the stroma of the marrow undergoes progressive change into fibrous tissue, similar to that seen in chronic osteomyelitis or osteitis fibrosa. The vessels of the marrow are thick and straight, and there is a diffuse fibrosis that is readily demonstrable with connective-tissue stains. This occasions a crowding out of the hemopoietic elements and results in aplasia, or perhaps it represents a response to a primary aplasia which gives rise to compensatory fibrosis.

Inflammation of Bone Marrow. This is rarely confined to the marrow, as it involves the bone as well and is known as "osteomyelitis."

Although usually due to pyogenic infections, notably staphylococcal, acute and chronic osteomyelitis may be produced by the action of other organisms. Among these are those of pneumonia, typhoid, plague, and other acute diseases and the virus of smallpox. The tubercle bacillus and *Treponema pallidum* may occasion infectious granulomas of the marrow and bone; miliary tuberculosis may seed out tubercles throughout the marrow, and gummas are occasionally observed. Hodgkin's disease may also cause marked changes in the marrow, but its diagnosis is not easy, as the Reed-Sternberg cells that typify it are al-

most identical in appearance with megakaryocytes. Usually there is a tremendous increase in cells resembling the latter, with marked eosinophilia and fibrosis which are not generalized but tend to be focal and to form nodular areas that are set off from the normal marrow, which may be utilized as a standard.

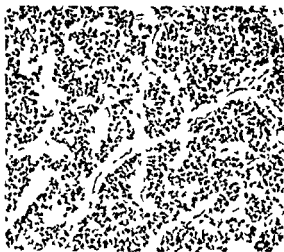
ACUTE OSTEOMYELITIS. In this, abscesses and hemorrhages develop in the spaces of the marrow and bring about thrombosis of the vessels, thus interfering with the nutrition of the bone and destroying its endosteum. The bone then becomes necrotic, and this process is far more spectacular than the conversion of the marrow into masses of pus. From the abscesses sinuses may develop and work their way to the surface where they penetrate the skin and discharge their contents. The healing process results in areas of cicatricial tissue in the marrow after the necrotic bone has been absorbed, discharged, or surgically removed. Bits of necrotic bone are known as "sequestra" and may take the form of long, flat, fenestrated and "worm-eaten" plates or tube-like structures.

CHRONIC OSTEOMYELITIS. When studied macroscopically or microscopically, this form of osteomyelitis is misleading, as very little may be observed that indicates extensive inflammation. When the apparently normal bone-chips are decalcified and sectioned they reveal that the marrow has been replaced by a loosely formed mass of fibrous tissue that may be very widely distributed. The bone is no longer living, but is necrotic, and its osteocytes either have disappeared or lie in their lacunae as shrivelled remnants of the usual plump osteocytes; their nuclei are pyknotic or broken up. Areas in the fibrotic marrow show granulation tissue, or persisting abscesses may be found. In its late stages the picture resembles osteitis fibrosa, excepting that most of the bone is dead.

Tumors of Bone Marrow. METASTASES. Carcinomas of certain organs, notably the prostate, breast, and lung, are prone to

surgery is indicated in this case, should there be any signs of recurrence

Macroscopically, this tumor is grayish, soft, and infiltrating. It may show a small focus within the shaft of the bone or in the body of a bone, connecting with a much larger mass that is infiltrating the soft parts in the vicinity. Microscopically it is seen to be made up of large, rather lymphoblastic elements that lie in large masses, or irreg-



Ewing's myeloblastic tumor of bone (from lower end of femur). Note masses of lymphoid cells surrounded by delimiting septa of connective tissue

ular alveoli surrounded by septa of stroma. The cells have no particular arrangement, although they occasionally form rosette-like grouping. Silver impregnation for the demonstration of reticulum shows that this tumor forms none, which would rule it out of the retothelial or endothelial category.

The presence of rosettes and retroperitoneal metastases have led some observers, notably Willis and Colwell, to consider the tumor a metastatic sympathoblastoma. The two cases of which these authors have published descriptions were certainly sympathoblastomas, but whether or not they were Ewing tumors is another question. Other observers have noted the rosettes and admitted that they were suggestive of Ewing's tumor, but they resolutely deny that the tumors that they have reported are sym-

pathoblastomas. Still other observers have come to the conclusion that the neoplasm is of lymphoblastic parentage and speak of "lymphoblastic myeloma." There the matter rests for the present. There are groups of excellent authorities in each camp.

MYELOMA. One may divide the myelomas into five groups: plasmocytic or plasma cell myeloma, myelocytoma, or myeloblastic myeloma, lymphocytoma, or lymphoblastic myeloma, erythroblastoma, and hemocytoblastic myeloma. As regards the derivation of these there may be differences of opinion.

All of the above tumors are malignant, and they apparently represent the development of hemopoietic cells into neoplastic elements. The development starts with the cells in various phases of their normal life cycle. For instance, the last one to be described, the hemocytoblastic myeloma, represents a tumor that starts "from scratch" from the most primitive and versatile cell in the marrow. The myeloblastic myeloma begins in myeloblasts or myelocytes and has not the potentiality for producing any members of the "red line" of cells. The plasmocytic myeloma for the present defies our attempts at identifying its ancestors.

These tumors are all highly unsatisfactory from the standpoint of therapy and present very poor prognoses; they are too widely disseminated for surgery, and as their origin is apparently multicentric they present no primary growth for early excision. Although they may show a good transient response to irradiation with the x-ray, the success of that treatment is very problematic, and most of the patients die without receiving much benefit from therapeutic measures.

Plasmocytic (Plasma cell) Myeloma. This is a multicentric tumor that affects a number of bones simultaneously, causing punched out defects in their osseous tissue like the holes in a Swiss cheese. These afford easy recognition of the growth when it is examined with the x-ray. The ribs and sternum are the chief sites of origin, the

Silver impregnations reveal a wealth of reticular fibrils interwoven among the cells. Very little marrow or adipose tissue is left intact, and the neoplasms are composed almost entirely of distorted reticular tissue. If bone is involved, which is not at all unusual, foreign-body giant cells may appear in considerable numbers. There are other forms of osteolytic sarcoma that are less readily aligned with the reticulum-celled group and may constitute a form of malignant giant-celled tumor. They are discussed under bony tumors.

VASCULAR TUMORS. The sinuses of the marrow are lined with reticulo-endothelium; hence tumors arising from these are similar to angiomas and angiosarcomas, but at the same time they take on many of the characteristics of reticulum-celled tumors. They tend to grow in masses and sheets that show indefinite vascular structure. Ewing recognized three types, all of them quasi-vascular.

Solitary or Telangiectatic Angio-endothelioma. This is a rare tumor chiefly affecting elderly subjects or adults and growing in the ends of long bones. It may pulsate, yield a bruit, and destroy bone. It grows relatively slowly, and under the microscope it reveals large, clear, cuboidal, or cylindrical cells arranged in columns or alveoloid spaces in which the blood circulates. Or it may grow in a more solid and less arranged manner, and because of its resemblance to hypernephroid tumors this indicates a careful examination of the renal region, both physical and roentgenologic, before a definite diagnosis can be decided upon.

Multiple Endothelioma of Bone. The term is from Ewing, who described this rare growth, citing one instance reported by Marckwald and indicating that a few others had been recorded. It is added here simply for the sake of completeness. This tumor is rare and may be found in nearly any bone in the body, being accompanied by symptoms of fever, pain, and cachexia. The wide distribution may be explained upon the

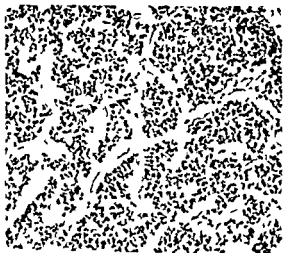
grounds that although active marrow may be limited to a few bones during adult life, the endothelial elements (reticular or vascular) remain in the adipose marrow. Although the symptoms suggest multiple myeloma, the microscopic picture differs from that of this neoplasm as it reveals masses of clear, polyhedral cells growing in sleeves about the vessels, possibly originating in the adventitial cells.

Ewing's Sarcoma of Bone (Diffuse Endothelioma of Bone, Endothelial Myeloma, Lymphoblastic Myeloma). Ewing made a very careful clinical and pathologic study of this neoplasm, which should go under his name until its true nature has been established. He persisted to the last in regarding it as an endothelioma, but there are reasons for questioning this concept which will be brought out presently. The growth is usually noted in young individuals, more than half the recorded cases occurring before the age of 20 and 80 per cent before that of 30. It usually affects the small and the flat bones, although it may arise at the ends of the long ones. It carries a high rate of mortality, concerning which Ewing makes the following statement: "In 24 fatal cases, the average duration of life was 19 months. In 54 cases, both dead and alive, the average duration was over three years. It is interesting to note that in one case, which died from other causes nine years after amputation, retroperitoneal lymphatic metastases were found at autopsy. Of the above 54 cases, 15 have survived more than four years after the onset of the disease. They were treated by amputation, alone or with radiation; by radiation, alone or with excision; and by radiation and toxins" (Coley's toxins were used.)

Dr. Ewing once told the writer that he considered amputation almost criminal when x-rays were so successful in treating this tumor, but there is reason to believe that his faith in the x-ray was somewhat shaken by later experience as the tumors began to recur. Probably preliminary x-ray therapy followed by prompt recourse to

surgery is indicated in this case, should there be any signs of recurrence

Macroscopically, this tumor is grayish, soft, and infiltrating. It may show a small focus within the shaft of the bone or in the body of a bone, connecting with a much larger mass that is infiltrating the soft parts in the vicinity. Microscopically it is seen to be made up of large, rather lymphoblastic elements that lie in large masses, or irreg-



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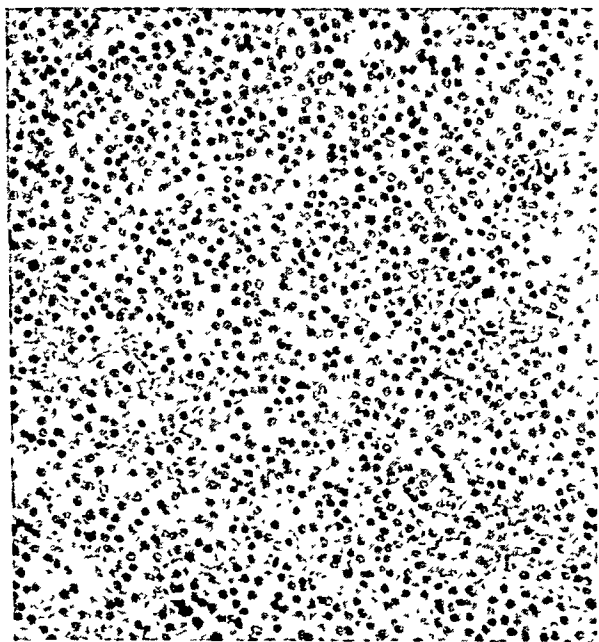
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other bones most frequently involved are the vertebrae, skull, femur, pelvis, and humerus, in that order. The growths vary in consistence; they may be waxy and semi-translucent or firm and opaque. Occurring chiefly in males between the end of young adulthood and early senescence, they occasion pain, fractures, and ultimate bony deformities. Albumosuria of the Bence-Jones



Plasmocytic myeloma, showing lack of architecture and resemblance of the type cells to plasma cells, which is characteristic.

type has been found in less than half of the cases, but this fact has been somewhat overlooked because it is so dramatic a sign when it is present in conjunction with the other typical characteristics. The serum proteins are elevated.

Microscopically the tumor is composed of cells which may resemble plasma cells very closely or may be slightly larger than these and show more delicate nuclei with a less pronounced "cart-wheel" arrangement of their chromosomes than do the plasma cells of inflammation. Furthermore, their cytoplasm may be less basophil than that of plasmocytes. Kaufmann considers the cells to be of reticulo-endothelial origin, and there have been others to take this view, which has something to be said in its favor. Ewing quotes cases reported by Craver and

Copeland in which the patients showed a fairly good condition of health almost up to the time of death; this is quite unlike the history of patients suffering from typical myeloma. The usual extension of the tumor to the lymph nodes was noted in these patients, but microscopic examination revealed reticulum-celled sarcoma in that situation. Such instances may indicate that there are two types of plasmocytomas; one of them is lymphoid and the other reticulo-endothelial (a convenient term for "reticulo-endothelial" devised by Roulet). Ewing leaves the decision to the reader.

At all events, plasmocytoma is a very characteristic tumor as a rule, and the microscopic diagnosis is usually very simple. The tumor is scattered in large masses throughout the microscopic field, replacing the normal tissue with cells that at least may be said to be very much like plasma cells—nearly enough like them to warrant calling the growth a "plasmocytoma." In passing, it should be noted that there is another plasmocytic tumor that usually develops in the lymphoid apparatus in the neck or in the tonsils or upper respiratory tract; this is composed of cells that are also very similar to plasma cells, but the growth is in quite another category and should not be confused with that of the bony skeleton. The treatment of plasmocytoma of bone is quite unsuccessful, and the prognosis is of the poorest.

Myeloblastic Myeloma (Myelocytoma). This arises from the hemopoietic cells of the marrow, and we may suppose that, as in other tumors, they reproduce part of the process of myelopoiesis in their mode of growth. Thus, a neoplasm arising from myeloblasts will consist chiefly of these cells and some of their derivatives as well. It is a confusing tumor, as it must be differentiated from various forms of myelogenous leukemia. The myeloblastic myeloma closely resembles the "leukosarcomas" of myelogenous leukemia, but the circulating blood, while it may show as many as 21 per

cent of myelocytes, reveals no other evidence of leukemia

Lymphoblastic Myeloma (Lymphocytoma) This exhibits widely disseminated growth in the bone marrow that generally resembles that of a plasmocytoma in its distribution, but is composed of fairly mature lymphocytes rather than plasmocytes. Some authors prefer to speak of this neoplasm as lymphosarcoma or medullary pseudoleukemia, which indicates some of the difficulty encountered when an attempt is made to classify the growth satisfactorily. Essentially it is a lymphosarcoma originating in bone marrow, and it would be only those who believe that this organ possesses no lymphoid tissue who would be much troubled by this assumption.

Erythroblastic Myeloma (Erythroblastoma) This resembles the other myelomas in its predilection for the marrow, but it may be found to be rather widespread in the body in sites where myelosis is prone to develop, such as the spleen, lymph nodes, and liver. It is rare, but occasionally bobs up in the laboratory. Microscopically it shows many immature forms of red cells which are recognized by their content of hemoglobin, best demonstrated in sections fixed in Zenker's fluid and stained by the Wolbach-Giemsa method.

Hemocytoblastic Myeloma One may very occasionally be confronted by myelomas that exhibit all the hemopoietic elements of the bone marrow in distorted, neoplastic form, including megakaryocytes. Only one of these has come under my observation in the course of some thirty years. They are very difficult to recognize in sections stained by ordinary methods, such as hematoxylin and eosin.

MYELOGENOUS LEUKEMIA Just as the lymphoid tissue has various forms of fixed tumors and a "floating" or circulating variety, and just as the latter may exhibit acute or immature and chronic or more mature forms, even so may the myelogenous tissue produce analogous types of circulating tu-

mors which are known as "myelogenous" leukemia.

Acute Myelogenous (Myeloblastic) Leukemia In this the myeloblast is the type cell which multiplies at such a rate that blood counts of 100,000 or more are not uncommon. The disease runs a rapidly fatal course and there is little time for the development of huge splenic enlargement or of adenopathy of a marked grade. There are anemia and progressive cachexia. The marrow, which is the primary site of the tumor, will be found to be gray and active where it should be largely adipose. Tumors may be produced in various parts of the body, in any organ, and particularly in the bones of the cranial vault, which is eroded by them so that there may be multiple, cushion-like masses over which the scalp is elevated and within which no bony resistance is palpable. This is because the masses occupy circular fenestra in the eroded bone.

The tumors, when sectioned, may be of a light grass green color—the so called "chloromas." The pigment fades rapidly, and the blocks fixed in formalin lose all their green color, which may be brought back if treated soon after fixation by immersion in peroxide of hydrogen. The nature of this pigment is still obscure. Under the microscope the marrow and the invaded organs will be found to be thronged with cells that might be (and frequently are) mistaken for lymphoblasts or monocytes. The nuclei of the three forms are all slightly different, the angles formed by the mitoses vary from very obtuse ones in the myeloblasts to more acute ones in the monocytes. This is a rather academic distinction, and the peroxidase reaction is more valuable. When it is carried out on smears of blood it is more satisfactory than it is in sections. It shows many coarse black or red granules (according to the method used) in the myeloblasts, few or no fine granules in the monocytes, and no granules in any of the lymphoblasts.

Chronic Myelogenous (Myelocytic) Leukemia This runs a longer and more leisurely course and has more time to produce

marked enlargement of the spleen (1,500 to 10,000 gm.) and of the various groups of lymph nodes, those of the axilla and groin being very prominent and striking. The disease resembles the acute form in many ways, but its microscopic picture differs in that the cells are myelocytes, rather than myeloblasts. They may be of the neu-



Area of leukemic infiltration in proximity of a renal glomerulus. This occurred during an exacerbation of chronic lymphogenous leukemia. (Army Medical Museum 65341.)

trophilic or eosinophilic form, and basophilic leukemia has been described, although Forkner doubts that it is an entity. Basophil myelocytes may be present in the other forms in remarkable numbers. Troublesome lesions develop in the skin and mucous membranes. In the former one may observe small nodules that have a microscopic similarity to the lesions of mycosis fungoides and must be distinguished from that disease. In the mouth there may be white patches on the mucous membrane of the gums and buccal surfaces that may break down and form ulcers. This is a very suggestive phenomenon that is so often present in leukemia that it should always

be suspected in the presence of intractable ulcers in the mouth. In the chronic form leukemic tumors are also commonly noted in any organ. The marrow is similar in appearance to that seen in the acute type of lesion, but under the microscope the cells are found to be the more mature myelocytes.

A strange feature of the disease is the fact that, should the patient contract a pneumonia or other disease characterized by polymorphonuclear exudates, these exudates occur as usual and their cells are the mature polymorphonuclear neutrophils rather than the immature myelocytes of leukemia. This is not invariably true, but it need not surprise the reader should he encounter such a phenomenon.

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marked enlargement of the spleen (1,500 to 10,000 gm.) and of the various groups of lymph nodes, those of the axilla and groin being very prominent and striking. The disease resembles the acute form in many ways, but its microscopic picture differs in that the cells are myelocytes, rather than myeloblasts. They may be of the neu-



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11

Lymph Nodes and Spleen

LYMPH NODES

HISTOLOGY

DEVELOPMENTAL DEFECTS

ACUTE INFLAMMATION

CHRONIC INFLAMMATION

TUMORS

METASTATIC

LYMPHOBLASTIC

RETOTHELIAL

EXTRAMEDULLARY PLASMACYTOMA

CIRCULATING

TUMORS (*Continued*)

PROGNOSIS

SPLEEN

HISTOLOGY

CONGENITAL ANOMALIES

TRAUMA

CYSTS

SPLENOMEGALY

INFLAMMATION

TUMORS

LYMPH NODES

Histology These are the happy hunting grounds of the surgical pathologist, for they are often removed for examination in connection with diagnosis, and the pathologist must be thoroughly familiar with their normal as well as their pathologic histology. There are three groups of lymph nodes in the body. First are those which are clustered as organoid complexes in the axillae, groins, triangles of the neck, and the hila of organs like the lung, liver, and spleen, and are scattered through the mesentery and like situations. The second group are integral parts of organs such as the tonsil, spleen, and intestinal tract. The third variety are normally either very inconspicuous or absent, they appear to develop in response to a variety of stimuli.

Lymph nodes are obviously catch basins or filters in the lymphatic drainage system, for we can trace this drainage from various parts of the body to the nodes. For example, the carbon inhaled with the atmosphere of smoky cities ultimately becomes concentrated in the hilar nodes of the lungs, some of the blood that is extravasated into an operative area will be found in the sinuses

of the regional lymph nodes within a matter of hours, serious infections of the extremities will, if unchecked, produce foci of acute infection in the regional chains of nodes serving these areas. Just what goes on in these nodes, however, is a matter for conjecture, it has been thought that there are two factors—mechanical and serologic. Organisms become caught in the pulp of the lymph node where they may be conveniently disposed of, and here toxins, flowing in the lymph stream, may be neutralized. The first hypothesis is fairly readily demonstrable, the second is largely a matter of a priori reasoning. As has been said in discussing inflammation, we know disgracefully little about the function and nature of the lymphocytes, and lymph nodes are almost entirely composed of these mysterious cells.

The normal lymph node is a small affair, about the size of a small white bean (7 × 4 × 4 mm), but it may become many times that size without being considered strikingly abnormal. There is a capsule surrounding the reniform structure, with a hilum at which large lymphatic channels enter and leave the node. The vascular supply, which is rather scanty, is composed of small, insignificant vessels that course in

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by pediculi, and near acutely inflamed organs like the gallbladder, appendix, or intestine

In the case of some acute infections, particularly typhoid fever, there is great activity on the part of the retothelium of the lymph sinuses ("sinus catarrh" of the German literature). Tularemia causes abscess-like lesions in which there are also many

In glanders one may see the same sort of necrotic lesion, on a slightly less violent scale, together with large cells (resembling neoplastic giant cells) that may be derived from the retothelial elements of the lymph node, these are called "malleus cells"

Another quasi acute reaction is that observed in lymphogranuloma venereum, in which the nodes of the inguinal chains may



Two lymphoid follicles from node exhibiting chronic lymphadenitis. Sinuses are not dilated and there is little retothelial proliferation. This distinguishes lymphadenitis from lymphadenosis.

macrophages, the picture partaking on the one hand of an acute inflammation with necrosis and abundant polymorphonuclear leukocytic reaction, while on the other hand it is reminiscent of the typhoid lesion in so far as there are very numerous macrophages present which tend to phagocytose other cells and, unlike those in typhoid, to surround areas of caseous necrosis. Thrombosis of the vessels of the node may be noted. A most violent acute lymphadenitis with extensive necrosis is seen in the lymph nodes in bubonic plague, and that disease derives its name from the swollen lymph nodes or "buboes" which it produces. The microscopic picture is one of devastating acute inflammation with massive necrosis

become very much enlarged and may be riddled with ragged, abscess-like foci and areas of somewhat caseous necrosis. Under the microscope these resemble a rather acute tuberculous infection, inasmuch as they exhibit palisading of macrophages about the periphery of a partly caseous, partly purulent focus in which polymorphonuclear leukocytes break down and set free innumerable small masses of nuclear material which have been mistaken for some sort of microorganism. As stated in the chapter on inflammation, a Frei test should be the deciding factor in this diagnosis. The lesions in this disease vary from the quasi acute type just described to more chronic forms.

the connective-tissue septa. The organ is made up of follicles of lymphoid tissue with central masses of lymphoblasts and retothelial cells known as "germinal centers." Sometimes one element predominates in these, sometimes the other. They are embedded in a spheroidal mass of lymphocytes and occasional lymphoblasts held together by a network of fibers of reticulin intimately connected with the retothelial cells which constitute the supporting matrix of the node. Among and between the follicles course channels lined with retothelium, the sinuses, which communicate with a peripheral or marginal sinus just beneath the capsule. This in turn is continuous with the lymphatic vessels at the hilum.

As lymph nodes "age," the core or medulla of the node becomes more and more fibrous and vascular and may contain large quantities of adipose tissue until, finally, the node becomes a large mass of fat contained in a thinned outer shell of lymphoid tissue a millimeter or two in diameter. This is often observed in the case of axillary nodes of obese elderly people in whom the enlarged "glands" may be mistaken for tumor metastases.

Before the pathology of the lymph nodes is considered it would be wise to sound a note of caution in regard to the choice of a site for excising biopsies of lymph nodes for surgical diagnosis. Because of its inconspicuous situation, the groin is all too often chosen for this purpose, and this is a pity because the groin is a drainage center for the products of inflammations of all sorts in the external genitalia. For that reason one will seldom obtain a lymph node that does not show the "historical landmarks" of a series of antecedent infections which obscure the lesion for which one is searching. It is far better, then, to select some other group, such as the axillary or cervical chains, for these nodes are less likely to be the site of chronic inflammation than are those of the inguinal region. Another point to stress is the fact that a patient with a diffuse adenopathy will present large and

typically involved lymph nodes together with smaller, more inconspicuously situated examples. The surgeon, seeking to avoid disfigurement, selects the small lymph node and presents the pathologist with a biopsy that may show nothing more than chronic inflammation. This necessitates the subsequent removal of one of the larger nodes. subjects the patient to further discomfort. and takes the time of the surgeon, while all of this might have been avoided had the large lymph node been excised in the first place.

Developmental Defects. On occasions, certain chains of lymph nodes may fail to develop, but this is uncommon. Very occasionally one may find epithelial rests in some of the cervical or retroperitoneal nodes. These rests, as a rule, are glandular and well developed; they do not resemble neoplasms because of their excellent differentiation and their rather widely scattered distribution, which avoids the lymph sinuses rather than occupying them, as metastases would do.

Acute Inflammation. Acute inflammation of the lymph nodes, or acute lymphadenitis, resembles acute inflammation elsewhere except for the fact that its presence in lymphoid tissue provokes lymphoid hyperplasia as a sequela. Grossly the organ is swollen and red; it is rather soft until it becomes so tense that it distends the capsule. It is succulent, and a milky fluid may be scraped from the sectioned surface. In the more advanced processes one may observe small yellowish abscesses in the parenchyma. Microscopically the sinuses are more or less flooded with polymorphonuclear leukocytes, the blood vessels are engorged, and there may be small abscesses composed of leukocytes in various stages of disintegration. This is the common picture in nodes that are infected by pyogenic cocci in connection with acute inflammation of the region that they drain. Thus, acutely inflamed lymph nodes may be observed near abscesses, in conjunction with infestations

prominent dark nucleoli with a cytoplasm that is coarsely granular and has a 'mucin like basophilic quality' The lymphoblasts are twice the size of these cells, and their cytoplasm, instead of being granular, is rather homogeneous and irregularly outlined There is marked proliferative activity in the pulp of the node, in contrast to most lymphoid lesions The phagocytes become eosinophilic but fail to form definite tubercles, although they may produce diffuse masses of epithelioid cells near the periphery of the node True eosinophilia may be noted in older lesions Ultimately the topography of the lymph node becomes obliterated, its sinuses compressed and distorted, so that the result readily leads to a mistaken diagnosis of lymphosarcoma As the type cell of infectious mononucleosis (the 'IM cell') has been shown to be a large, atypical lymphocyte, this mistake is readily comprehensible The proliferation of retothelium may simulate diffuse tuberculosis, while the eosinophilia and large macrophages may mislead one into considering Hodgkin's granuloma

Infectious mononucleosis, then, affords a lesion that is best diagnosed in conjunction with a good clinical history, without which the pathologist is never quite sure of his ground A story of an acute attack of sore throat, with swollen cervical nodes and fever and malaise, together with a high 'mononuclear' differential and no evidence of leukemia, materially aids the diagnosis A lymph node with an indefinite architecture and large numbers of lymphoid cells with vesicular nuclei, mitotic figures, and a granular cytoplasm, together with a tendency to form groups, should arouse one's suspicion of mononucleosis

Infectious Lymphocytosis This is a newly described infectious disease which occurs in children and gives rise to few if any symptoms The child may be a bit listless and may or may not have a little fever and sore throat the attention of the physician is sharply drawn to the fact that the blood shows sufficient lymphocytes in the smears

(sometimes 100,000 per cu mm) to arouse suspicion of chronic lymphogenous leukemia Unlike the cells of infectious mononucleosis, however, these lymphocytes are not in any way abnormal, there is no generalized adenopathy and the spleen is not enlarged as it may be in that disease Smears of the bone marrow show an increased number of normal lymphocytes

Biopsies from lymph nodes are most surprising, the nodes are not abnormal looking, as they are small and rather flabby, but under the microscope they show normally active follicles which may reveal some hyalin degeneration, and in the sinuses there is a very conspicuous proliferation of retothelial cells until the channels are almost choked with them In some cases, where the chief complaint is abdominal pain, there is a question as to whether the mesenteric nodes are or are not enlarged The pathologic picture of infectious lymphocytosis, then, is paradoxical the lymph nodes which should normally produce lymphocytes are hypoplastic except for their reticuloendothelial elements, while the blood shows an almost leukemic lymphocytosis This must indicate that these cells proceed from the marrow, which alone shows hyperplasia of lymphoid elements

The disease has just been described by C H Smith, and our knowledge thereof is as yet limited, as children do not die of it no autopsy material has as yet been studied, and as it does not make them very sick it may go completely unnoticed unless blood counts in the course of routine reveal its presence

INFECTIOUS GRANULOMAS Tuberculous Lymphadenitis The unit lesion of this is the typical tubercle caused by the *micro bacillus tuberculosis* a grouping of epithelioid cells or macrophages into spheroidal complexes with Langhans giant cells among them and possibly caseation of the more central elements of the masses The lesion is usually surrounded by a zone of lymphocytes Tubercles may be milary, conglomerate, or caseous, depending upon their age

Chronic Inflammation. There are two general groups of chronic lymphadenitis: "chronic lymphadenitis" (subdivisible into chronic lymphadenitis proper and chronic lymphadenosis) and "specific chronic lymphadenitis," which may be subdivided into a number of types according to the etiologic agent involved.



Section of lymph node showing chronic "lymphadenitis." There is little hyperplasia of lymphoid tissue, while retothelium of lymph sinuses is definitely increased in amount and sinuses are dilated and prominent. (Compare with illustration of "lymphadenitis.")

CHRONIC LYMPHADENITIS PROPER. This is seen in any chronic inflammation that spreads to regional nodes, which are enlarged and moderately firm and may look sarcomatous on section, being homogeneous and light brown. Microscopically there is great hyperplasia and phagocytic activity in the follicles and a general washing out of normal topography by an inundation of the tissue with lymphocytes, chiefly of the small variety. The sinuses are filled with them and there are a few lymphoblasts among them. The hyperplasia of the follicles may be so marked as to simulate nodular sarcoma.

CHRONIC LYMPHADENOSIS. The inflammatory factor in this is not as evident as in chronic lymphadenitis. On gross examination the lesion differs little from that de-

scribed above, but under the microscope there are striking dissimilarities. The hyperplasia centers in the retothelium of the sinuses, which proliferates to such a degree that the masses of cells resemble those of a metastatic carcinoma and must be carefully distinguished therefrom. The lymphoid tissue, on the other hand, may be fairly normal or even atrophic. Such a picture is commonly seen in nodes that drain an operative site, in which case numerous erythrocytes will be found in the sinuses, where they are being phagocytosed by macrophages.

Lymphadenosis appears to follow aseptic and hemorrhagic lesions in the neighborhood of the nodes involved and represents one of the depots for the clearing up and disposal of debris. Axillary nodes removed during radical mastectomies will often show this picture without manifesting any evidence of metastasis, so that one must be familiar with it and be able to distinguish retothelial proliferation from epithelial metastases; otherwise a mistaken diagnosis will cloud an otherwise favorable prognosis. The retothelial cells are paler, their nuclei more vesicular, and in sections stained by the Masson technic they tend to take on a slightly greenish color in their cytoplasm, while that of epithelial cells stains red.

SPECIFIC CHRONIC LYMPHADENITIS. *Infectious Mononucleosis.* Although the disease that bears this name is acute the lesions it creates in the lymph nodes are of a more chronic nature and are not readily recognized. It is imperative to study them in sections stained by the Giemsa method or with phloxin and methylene blue after Zenker-fixation.

Gall and Stout outline the following characteristics as diagnostic. The lesion is the result of proliferative stimuli, so that the germinal centers become hyperplastic and show large secondary nodules composed of actively growing lymphoblasts and macrophages. The tissue becomes crowded with lymphoblasts and with a smaller variety supposed to be pathognomonic of the disease; these have large vesicular nuclei and

omas) The malady itself was for a long time considered as a tubercloid of the skin, and it is only within the past decade or so that it has been recognized as a generalized disease. The lymph nodes show tubercles that closely resemble those of tuberculosis, particularly when viewed with the unaided eye. To summarize the microscopic characteristics (which differ a good deal from those of the true tubercle) it should be pointed out that the lesion is fibrotic, caseation does not occur, the giant cells may contain "asteroid bodies," and the Boeck's tubercles are not apt to coalesce and constitute conglomerate forms. They are as strikingly numerous as those of a very acute miliary tuberculous lesion, and are fairly evenly distributed throughout the lymph node. They have serpiginous outlines and all their components stain clearly, and appear to be in prime condition, this is in contrast to those of the epithelioid cells of true tuberculosis, many of which have a degenerated appearance.

Xanthogranuloma of Lymph Nodes This is a rare and poorly understood condition. Its lesions resemble a combination of tuberculosis and Boeck's sarcoid with the added feature of large numbers of foam cells, or "lipophages." Like Boeck's sarcoid it may cause cutaneous lesions which are reddened, papular swellings resembling boils but almost stony hard and practically painless. They appear and disappear on any part of the integument. In the lymph nodes the disease causes lesions that, in the gross, are practically indistinguishable from those of tuberculosis. Under the microscope there are tubercles composed of epithelioid elements and giant cells, but there are also wide fields of vacuolated foam cells like those of a xanthoma, and plasma cells abound in the tissue between the tubercles, producing large numbers of Russell bodies. Necrosis develops at the center of the lesions and may be caseous or purulent.

I have seen but one such case—a patient with innumerable dermal lesions and, during one attack, involvement of axillary

lymph nodes which was misdiagnosed elsewhere as "atypical tuberculosis." A careful bacteriologic study of the lesions resulted in the cultivation of only an anaerobic form of actinomyces. Oberling has studied this and similar lesions and has given them the name "xanthogranuloma", a few cases have been reported in personal correspondence from New Orleans and Baltimore.

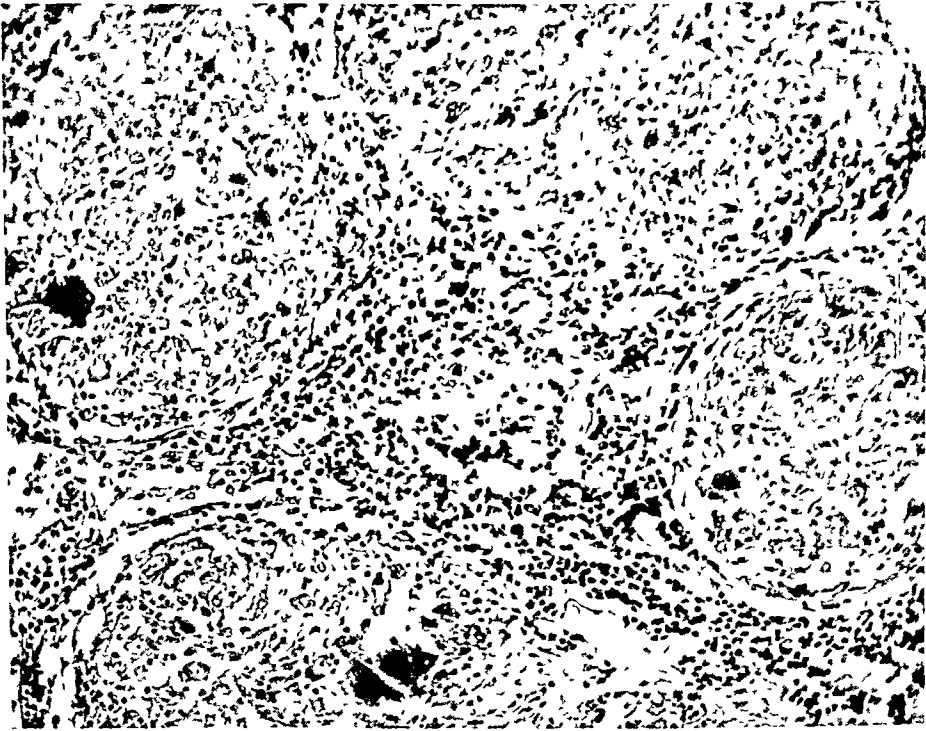
Syphilis of Lymph Nodes In the primary stage the inguinal nodes may be enlarged, hard, and painless. Microscopically they exhibit proliferation of the sinus endothelium and huge numbers of treponemata. While the inguinal, epitrochlear, axillary, and submaxillary nodes are affected in this stage, there is a generalized lymphadenopathy of an exactly similar type in the secondary stage. In the tertiary form gumma may develop, but this is very rarely seen in the laboratory. If one suspects a lesion of being syphilitic one should be careful to inspect the vessels for signs of angitis, which may be acute and characteristic in many instances, with proliferation of the vascular endothelium, polymorphonuclear leukocytes in the vessels and their walls, and accumulations of lymphocytes and a few polymorphonuclears in the perivascular tissue. Such vascular lesions aid materially in making a diagnosis. Academically speaking, the gumma is more lymphocytic and less epithelioid in its composition, a peripheral line of undulating elastic tissue may be demonstrated with appropriate stains, its similarity to the elastic laminae of arteries indicating the intravascular situation of the gumma. The necrosis in the gumma is "gummy" and not "cheesy", more politely expressed it is gummatous and retains the outlines of the destroyed tissue, rather than being caseous and obliterating all the architectural topography.

Hodgkin's Disease of Lymph Nodes This disease occupies a position between that of inflammation and that of neoplasia, so it should be discussed before we take up the tumors of the lymphoid apparatus. For many years investigators have been

A lymph node affected by tuberculosis will be large and swollen and will show yellowish tubercles which, as they become larger, undergo central cheesy degeneration or caseation. With mixed infection some pus may be present. The lesions fuse and the caseation converts the entire node into a sac of yellowish, curdy material with a cap-

occasionally be accomplished with prolonged searching, but one is usually forced to make the diagnosis on the basis of typical morphology; if the morphology is atypical one must fall back on clinical support.

Tuberculous lymphadenitis, formerly called "scrofula," affects lymph nodes in any part of the body but favors the cervical



Typical lesion of Boeck's sarcoid in lymph node of supraclavicular region. Lack of caseation is to be noted. Tubercles are almost perfectly spherical and contain goodly amount of collagenous fibrous tissue.

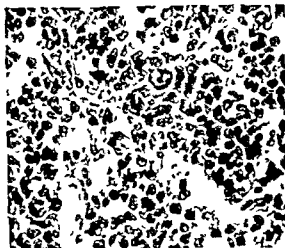
sule of fibrous tissue. As this heals (which it frequently does) calcification may set in, this is at first chalky but ultimately as firm as marble.

Tuberculosis sometimes causes a diffuse proliferation of the reticulum with branching cords of epithelioid cells and increase in reticulum and fibrous tissue without the formation of very definite tubercles. This is "diffuse fibrous tuberculosis"; it is rather rare and may be mistaken for sarcoma or infectious mononucleosis. It would be gratifying to state that a carbol-fuchsin stain would infallibly demonstrate *M. tuberculosis* and decide the diagnosis, but the organism is notoriously difficult to demonstrate in lesions of lymph nodes. It can

and mesenteric chains. In the former it is apt to commence high and to progress downward, giving the neck a conical form with the base upward; this is in sharp contrast to the cervical manifestations in Hodgkin's disease, which begins low and progresses upward, producing a deceptively muscular-looking neck with the base of the cone at the bottom. The question as to whether tuberculous lymphadenitis is usually caused by the bovine or the human strains of *M. tuberculosis* is of little importance here; it will be found fully discussed in textbooks of a more general type.

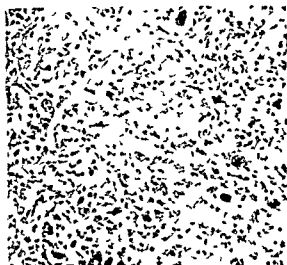
Boeck's Sarcoid. The lesion of this disease has been discussed in Chapter 2 under Chronic Inflammation (Infectious Granu-

amount of cytoplasm, and a characteristic nucleus that is large and vesicular and that becomes progressively lobulated until it

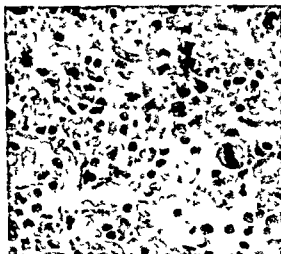


High dry magnification of field from granulomatous Hodgkin's lesion in lymph node showing typical Reed Sternberg cells at upper center of field

thelium which may proliferate actively and produce multinucleated giant cells much like those of Langhans. This is confusing, not only because the cells resemble those of tuberculosis but because tuberculosis and Hodgkin's disease have often existed simultaneously in one lymph node. This led to the supposition at one time that Hodgkin's disease might be caused by a mutant of the *M. tuberculosis*.



Typical lesion of Hodgkin's disease in lymph node. Note large Reed-Sternberg giant cells and granulomatous background.



High powered photomicrograph of lesion of pleomorphic type of Hodgkin's disease in lymph node. Most cells are of distorted Reed-Sternberg giant cell type.

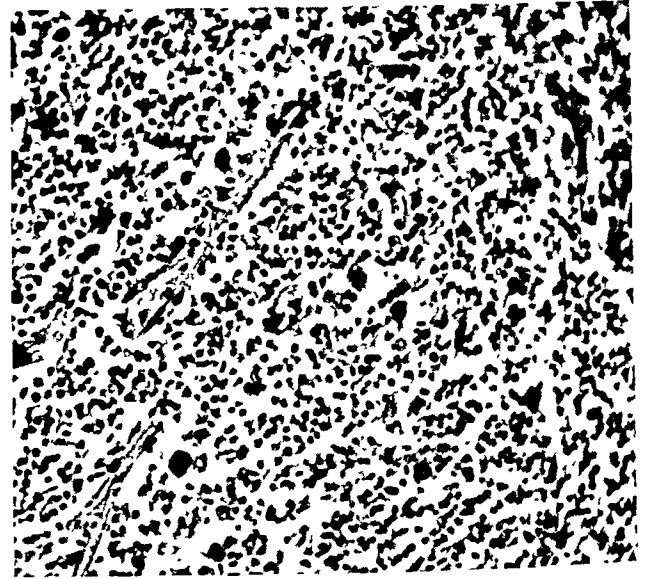
One may thus observe lesions that are granulomatous, others that show increasing numbers of Reed-Sternberg cells and are more neoplastic in their appearance, and finally, lesions that show such large numbers of these cells in mitosis and exhibiting very bizarre forms that the picture is that of a sarcoma and the type is known as "Hodgkin's sarcoma." This almost exactly resembles the pleomorphic forms of lympho- and retothelial sarcoma, a fact that brings the three conditions closely together at one phase of their development. All this, naturally, speaks for the neoplastic nature of Hodgkin's disease. The diagnosis is made, under such circumstances, upon the basis of the presence or absence of eosinophils, which are part of the "Hodgkin's trinity" and are

undergoes several divisions without division of the cell itself. This produces a multinucleated giant cell that is indistinguishable from any of a number of neoplastic giant cells. Along with these changes there is a variable response on the part of the ret-

isolating organisms from these lesions without proving their case with any definiteness. Bunting and Yates isolated a diphtheroid bacillus, L'Esperance produced Hodgkin's-like lesions in fowls by injecting material from triturated lesions of human lymph nodes. Poston and Parsons found *Brucella melitensis* in about half of the lesions examined bacteriologically, but Forbus and Gunter were unable to demonstrate that this organism was the etiologic agent in Hodgkin's disease, although it appeared to be a fairly regular concomitant thereof. Many years ago Mallory advanced the theory that this malady was a tumor; more specifically, that it was a sclerotic form of lymphosarcoma. His pupils have always kept this in mind, one of them (Medlar) suggesting that the condition might be a form of megakaryocytic leukemia. He based his idea upon the morphologic similarity between the Reed-Sternberg giant cell that typifies Hodgkin's granuloma and the megakaryocytes of the bone marrow. Hodgkin's disease certainly runs a clinical course that is very similar to that of lymphosarcoma through its marked generalized adenopathy, its great (if transient) susceptibility to x-irradiation, and its general downhill and fatal course. Its tendency to provoke bouts of spiking fever with fairly long remissions (Pel-Ebstein fever) suggests an infection, but since as far as we know it is not transmissible from one individual to another, this means little.

Grossly the malady causes an insidious enlargement of lymph nodes which may be generalized or confined to certain chains. For example, it may be rather sharply limited to the peritoneal cavity for some time before appearing elsewhere, in which case the spleen is enlarged and shows typical lesions. This is known as "splenic Hodgkin's disease." It may be limited to the retroperitoneal nodes where, alone, typical lesions are found, while the spleen and liver exhibit vague aberrance from normal and the systemic lymph nodes appear to be quite normal everywhere save in this one

retroperitoneal group. It may produce foci resembling neoplastic metastases in situations where lymph nodes are not normally prominent, like the spinal canal. The typical case usually shows progressive enlargement of the nodes in the neck which begins below and works upward, as described in the dis-



Granulomatous type of Hodgkin's disease in lymph node. Large cells are Reed-Sternberg giant cells that typify the lesion.

cussion of tuberculous lymphadenitis. The nodes may become much enlarged, measuring as much as 6 x 4 x 3 cm.; on section they are yellowish-brown or almost white and rather granular; there may be barely visible fibrous trabeculae. In advanced cases one may see areas of necrosis that have serpiginous or "geographic" outlines, but these appear to be rarer than formerly, probably because of earlier recognition and treatment by x-ray.

The microscopic appearance of the "Hodgkin's node" runs the gamut from a granulomatous to a frankly neoplastic lesion; in the former there are large numbers of eosinophils, a variable amount of fibrosis, and small numbers of the cells that typify Hodgkin's disease. These are the "Reed-Sternberg" giant cells described almost simultaneously by Dorothy Reed in this country and Sternberg in Vienna. They are much larger than lymphoblasts, have a varying

dence of metastasis in its lymphoid tissue, upon which so much of the prognosis will hinge. Gastric tumors metastasize to the lymph nodes of the omentum, usually being found along their gastric attachments to the greater and lesser curvatures. Carcinomas of bronchial origin will be found metastasizing to the hilar nodes of the lung. The late and infrequent metastasis of colonic carcinoma is one of the reasons for the ex-

istence of lymphocytes of a neoplastic sort to lymph nodes not yet, or not at all, involved as primary sites. This is noted in some forms of lymphogenous leukemia, in one instance in the case of a lymphosarcoma of the thymus that occasioned that disease without the systemic lymph nodes playing any apparent role as primary sites.

Lymphosarcoma The primary tumors of the lymph nodes may be subdivided into



Typical nodular lymphosarcoma, known also as "giant folliculoma" and "Brill Symmers' disease." Note very large spherical nodules that resemble lymphoid follicles and characterize the lesion, they frequently coalesce.

cellent surgical results obtained through operations on the sigmoid, rectum, etc.

But metastasis may not be confined to regional nodes alone, one may observe that which might be called "telemetastases," in which daughter tumors are found at a great distance from the primary focus. Thus one often notes metastatic carcinoma in one or more of the lymph nodes of the lower end of the cervical chains, particularly in a supraclavicular node on the left which, when invaded, is known as "Virchow's node" and usually indicates the presence of gastric carcinoma.

Other tumors (sarcomas among them) metastasize to lymph nodes. A very confusing type of this process may be the metastasis

of lymphocytes of a neoplastic sort to lymph nodes not yet, or not at all, involved as primary sites. This is noted in some forms of lymphogenous leukemia, in one instance in the case of a lymphosarcoma of the thymus that occasioned that disease without the systemic lymph nodes playing any apparent role as primary sites.

TUMORS DERIVED FROM LYMPHOID TISSUE
Lymphoma and Lymphosarcoma A malignant tumor of lymphoid tissue, if it is a lymphoma, is theoretically a neoplasm of lymphocytes, but it would be more correct to say that the lesion of chronic lymphadenitis is the

not seen in great numbers in the other conditions, although they may not be entirely absent therefrom. The "Gordon test," in which fatal paralysis was produced in rabbits by the injection of extracts of lymph nodes from Hodgkin's disease, was thought to be diagnostic until it was shown that extracts of normal bone marrow would bring about the same results. This was attributed to the presence of products of decomposition originating in eosinophils in both types of extract. If Hodgkin's disease runs a slow and chronic course, or if there has been intensive irradiation, a marked fibrosis supervenes and the nodes become coarsely scarred and very fibrous. In them it is often difficult to find enough lymphoid tissue upon which to base a microscopic diagnosis.

Before making a diagnosis, then, one should always find some Reed-Sternberg cells; they are a *sine qua non* in this respect. A goodly exudate of eosinophils with a variable amount of fibrosis completes the diagnosis, although one or the other of these two characteristics may be missing in atypical lesions which, very unfortunately, are much more common than the typical variety. The origin of the Reed-Sternberg cell is still uncertain; commonly attributed to the reticulo-endothelial group, its heavily stained chromosomes, large nucleolus, and basophil cytoplasm indicate that it may be of lymphoblastic origin. This question has never been satisfactorily settled.

Lymph Nodes in Disseminated Lupus Erythematosus. It has been known since 1907 that there are specific changes in the lymph nodes in this disease. Short gave a brief description of large cells that may be multinucleated and may show mitotic figures. Ginzler and Fox described these in more minute detail and listed changes that vary from edema and sinus hyperplasia (which are not specific lesions) to inflammatory reactions characterized by the presence of many histiocytic cells and a few plasmocytes and polymorphonuclear leukocytes. A number of observers have noted necrobiotic changes.

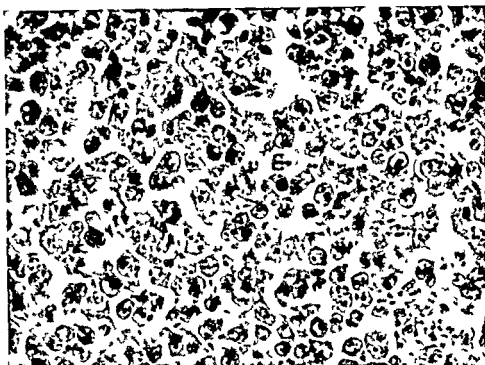
In 1943 Fox and Rosahn published an excellently illustrated description that goes far to prove that there is a rather elusive specific lesion. There is distortion of the lymphoid architecture and engorgement of the sinuses by fluid; the follicles are destroyed, the sinuses become distended by numbers of lymphocytes, plasmocytes, and retothelial cells. Polymorphonuclears are not numerous and eosinophils are supposedly rare, although I have seen cases where they were plentiful enough to mislead me into diagnosing Hodgkin's granuloma. Fox and Rosahn place weight upon the presence of a large cell that is three or four times the size of a lymphocyte, neutrophil to eosinophil in its cytoplasmic-staining reaction, and not unlike a megakaryocyte. It has a large multilobular nucleus, and two or more of these nuclei may be noted in a cell. Its cytoplasm is homogeneous and free from vacuoles. Thus it may readily be confused with the large cells of infectious mononucleosis or the Reed-Sternberg cell. Fibrosis is not a feature, being present only in scattered foci. The blood vessels may show the fibrinoid degeneration that is typical of disseminated lupus erythematosus. Special stains add nothing to the picture. The large number of plasmocytes and the clinical history of the case will assist one in coming to a conclusion, and the vascular degeneration is an added help when found.

TUMORS OF LYMPH NODES AND LYMPHOID TISSUE

Metastatic Neoplasms. By far the most frequently encountered tumors of lymph nodes are those that arise elsewhere and represent metastases in these organs; as metastasis via the lymphatics is most commonly noted in the epithelial tumors they are usually carcinomatous rather than sarcomatous. It is of the utmost importance, when inspecting a given specimen of carcinoma, to look into the condition of the attacked regional lymph nodes. Thus, in the case of mammary carcinoma, the axillary fat should be carefully searched for evi-

sarcomas and Hodgkin's disease look alike, but microscopically they are quite different from one another. Besides the rapidly dividing lymphoblasts in the lymphoblastic sarcoma, one may find an occasional neoplastic giant cell closely resembling that of Reed and Sternberg, while Hodgkin's disease may further be simulated by the fact

ing microscopic picture. It is composed of cells of every imaginable size and shape, vaguely resembling lymphoblasts, but so bloated and distorted that they take on a very "malignant" appearance. (The quotation marks are used because many of the neoplasms of any type whatsoever that may appear very strange and bizarre are



Lymphoblastic form of lymphosarcoma comprising cells that are more like lymphoblasts than like mature lymphocytes. Note numerous, rather regular mitotic figures.

that one may note a few eosinophils. These, however, are seldom numerous enough to cause much confusion. As already noted, nodular lymphosarcoma may (by the fusion of the giant follicle) become transformed into the lymphoblastic type now under discussion. Although this form represents a more youthful stage in the history of the lymphocyte and would correspond with acute lymphogenous leukemia," it differs from the more mature lymphocytic lymphosarcoma chiefly in running a more rapidly fatal course.

Pleomorphic Lymphosarcoma. While this does not differ from the other forms in its gross characteristics it presents a most strik-

ing microscopic picture. It is composed of cells of every imaginable size and shape, vaguely resembling lymphoblasts, but so bloated and distorted that they take on a very "malignant" appearance. (The quotation marks are used because many of the neoplasms of any type whatsoever that may appear very strange and bizarre are

not, on that account, to be considered any more clinically malignant than many a fairly well differentiated neoplasm.) In the pleomorphic lymphosarcoma, multinucleated cells are numerous and those with lobulated nuclei are even more so, thus the tumor resembles Hodgkin's sarcoma very closely, and it is often hazardous to attempt to distinguish between them. Eosinophils are absent, as a rule, and there is no fibrosis in the case of the lymphosarcoma, these are trifling differences.

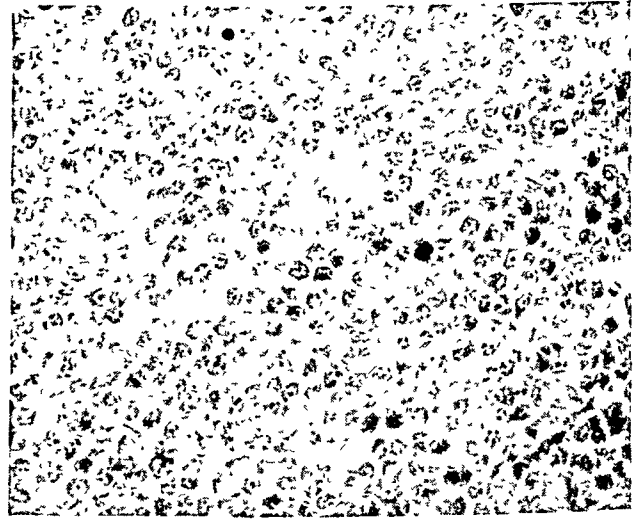
TUMORS DERIVED FROM RETOTHELIUM
Primitive Retothelial Sarcoma (Reticulum cell Sarcoma, Primary Endothelioma of Lymph Nodes, Reticulo endothelial Sar-

would be uncertain that it really did exist. If one large lymphoid tumor were found in a chain of normal nodes one might venture to call it a lymphoma, but one practically never encounters such growths.

Nodular Lymphosarcoma (*Giant Folliculoma*, *Giant-follicle Lymphosarcoma*, *Brill-Symmers' disease*). The earliest definite lymphoid tumor with which we are familiar is one in which the follicles become conspicuously enlarged until, as time goes on, they may fuse and produce the lymphoblastic lymphosarcoma described later. These nodular tumors have no characteristic gross appearance; they are homogeneous and white and resemble much overgrown lymph nodes. They are often slowly growing, appearing in middle-aged people, running a long course, and apparently lowering the resistance of the patient, who may die of intercurrent infection. They may, however, become rapidly growing and develop into lymphoblastic sarcomas. Their microscopic appearance is striking; the large, pale follicles stand out prominently as lighter areas in the darker lymphoid pulp. They may simulate the appearance of the follicular hyperplasia of chronic lymphadenitis, but in that condition one usually finds actively phagocytic macrophages in the germinal centers, while in nodular lymphosarcoma such phagocytosis is absent and the germinal centers are composed of masses of cells like neoplastic, overdeveloped lymphoblasts. With time, this neoplasm may undergo remissions, and fibrotic changes may supervene and appear to arrest the symptoms and the development of the lesion. On the other hand, the follicles may fuse until the entire node is converted into a lymphoblastic lymphosarcoma, which runs its usual fatal course.

Lymphocytic Lymphosarcoma. In this form we have an analogue of "chronic lymphogenous leukemia" inasmuch as the typical cell is the lymphocyte, which may look very normal or may be slightly larger and more darkly staining than normal. There is an overgrowth of these cells until the

entire node becomes flooded with them and all topography disappears. This gives the tumor two gross characteristics: it is enlarged and its sectioned surface is whitish and finely granular or slightly tinged with brown. The nodes may be universally affected, or single chains alone may be attacked; usually the adenopathy is generalized. The microscopic picture consists of a reproductive insurrection of lymphocytes



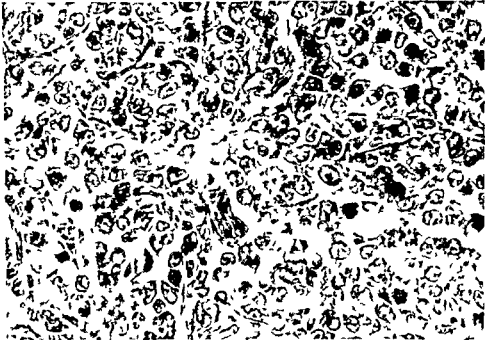
Lymphocytic lymphosarcoma in lymph node. Most cells simulate small lymphocytes, and one of these (lower right middle) is in mitosis. This is a diagnostic point of value.

that results in a complete inundation of the lymph node. The germinal centers are obscured or invisible, and one finds small lymphocytes everywhere, including the tissue of the capsule and that just outside of it. A striking and diagnostic feature is the presence of mitotic figures in the lymphocytes which, under normal circumstances, are produced as "end results" by the lymphoblasts and are supposedly incapable of mitosis. Thus far this characteristic has been found to be of great assistance in making a diagnosis.

Lymphoblastic Lymphosarcoma. In this we have the transformation of the lymph node into a mass of rapidly growing lymphoblasts similar to those seen in the normal germinal centers but probably fundamentally different. In the gross all lympho-

coma) Ewing first described this as "primary endothelioma of lymph nodes" In its gross appearance it is not unlike lympho sarcoma, but microscopically it is strikingly different and exhibits two types of growth a diffuse overgrowth of neoplastic reticulum cells throughout the lymphoid tissue which they gradually replace, and a more concentrated and focal overgrowth of the same

primitive retothelial sarcoma is the monocyctoma, which has been recognized relatively recently by Hu This, in addition to showing very similar characteristics, exhibits the staining peculiarities that are shown by monocytes when the tumor is subjected to supravital staining with neutral red and Janus green There is the rather compact cytoplasm and the typical rosette of gran



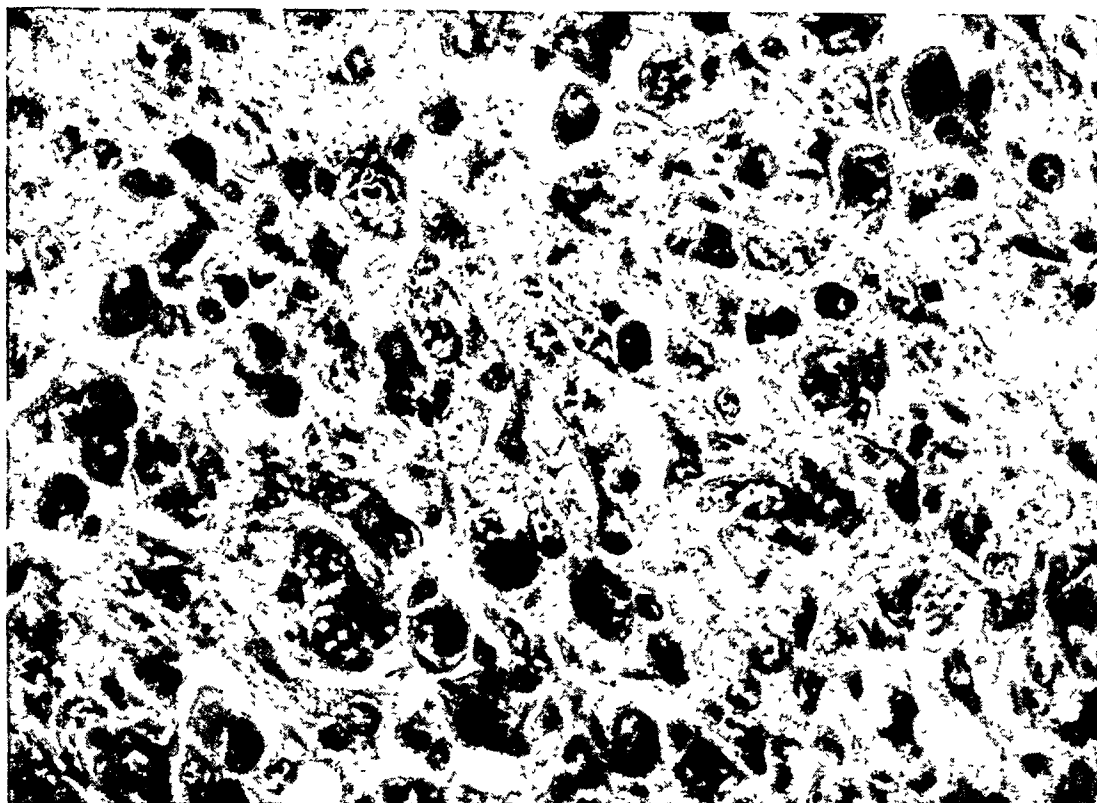
High powered view of primitive retothelial (reticulo endothelial) sarcoma Note vesicular nuclei, mitotic figures, and the somewhat stippled and sometimes generous cytoplasm of cells

sort of cells which congregate in masses that have an epithelial appearance Thus they may resemble metastatic carcinoma very closely, and it is only by careful attention to staining technic that they may be differentiated

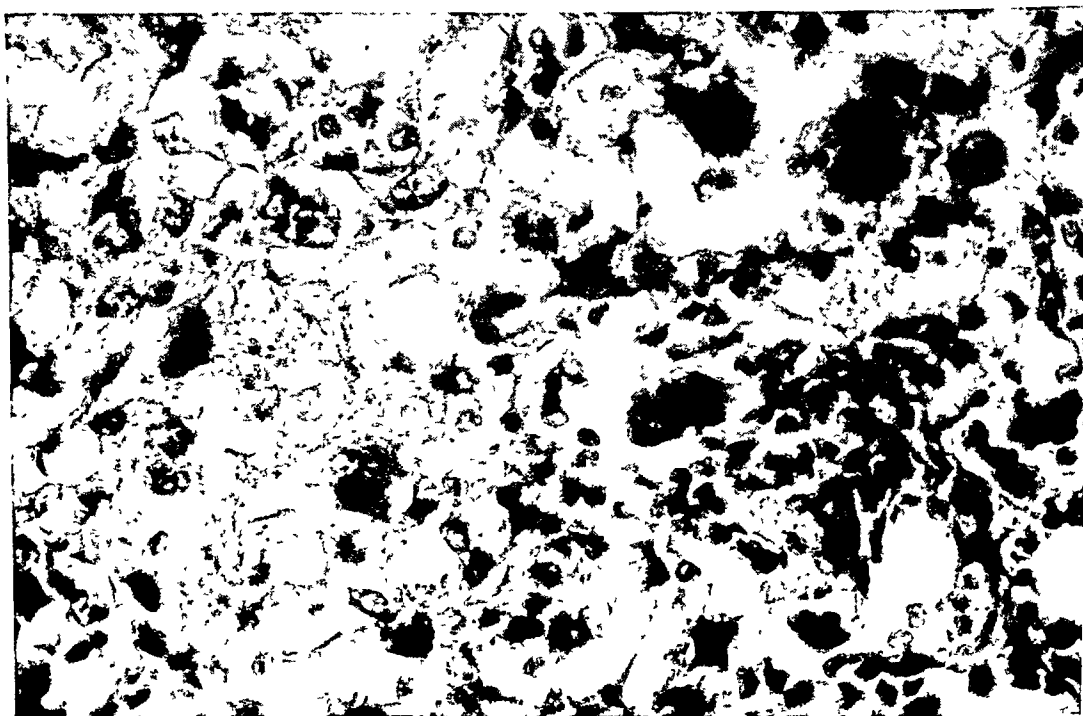
In either of the two forms just described the cellular units are pale and have vesicular nuclei with prominent nucleoli In impregnations with silver a reticulum of fine black fibers is found to form a felting among and around the cells, even when these are massed into the second type of architecture the reticulum will be found throughout the mass not merely outlining it with a stout basement membrane, as would be the case in carcinoma A subvariety of the

ules in the light of the nucleus that was described by Cunningham, Sabin, and Doane Furthermore, it has been noted in our laboratory that the cells take on a granular impregnation with silver (argyrophilia) similar to that noted in the "dust cell" of the pulmonary alveoli Whether or not this subvariety should be split off from the "primitive" group is a matter of taste and of rather limited academic interest, as the tumor behaves much like the primitive retothelial sarcoma Probably it should be considered as something a little different from ordinary retothelial sarcoma

Pleomorphic Retothelial Sarcoma This type (in our experience, at least) usually affects only a single chain of lymph nodes



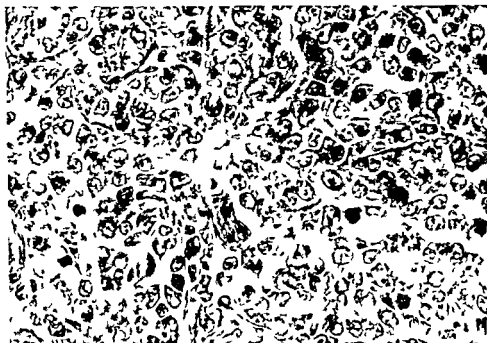
Pleomorphic type of lymphosarcoma that approaches retothelial and Hodgkin's sarcomas in its appearance. It shows many neoplastic giant cells and unorthodox mitotic figures, and its cells are all much larger than lymphoblasts.



Pleomorphic anastomotic type of retothelial sarcoma in which cells are a travesty on those of supporting retothelium of lymphoid tissue.

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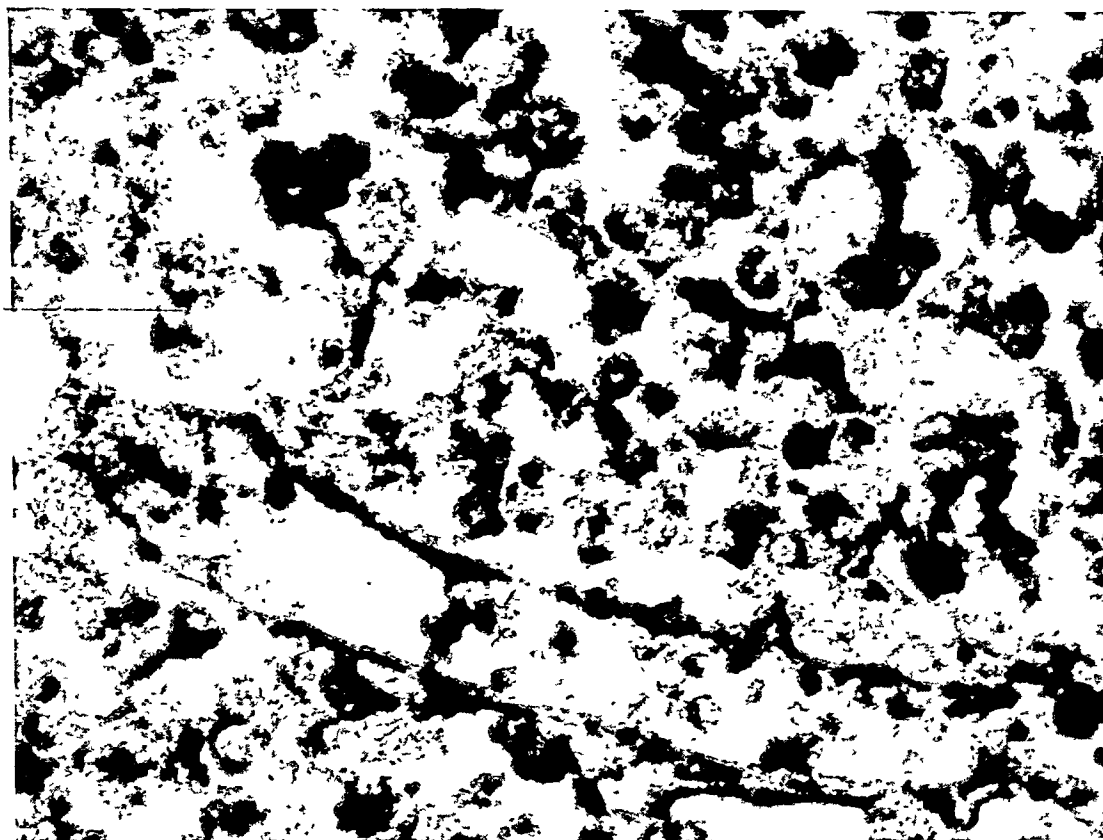
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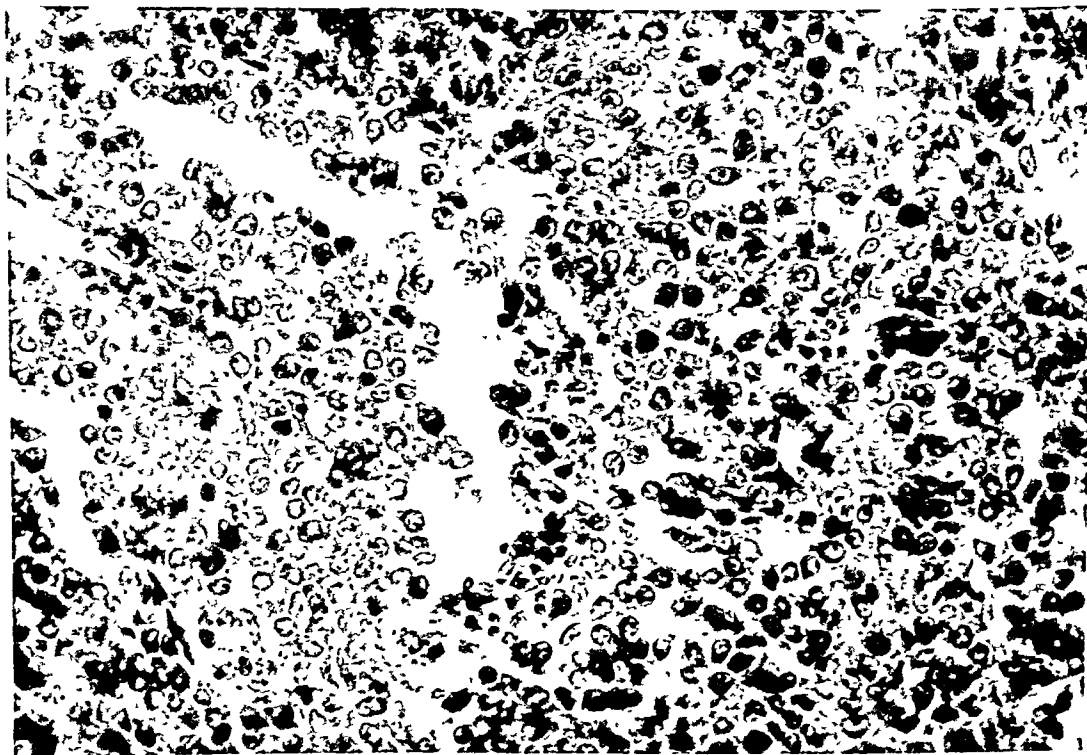
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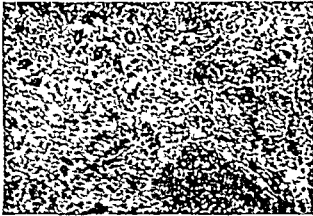


Monocytic sarcoma (a type of retothelial sarcoma) in which cells are impregnated with silver to demonstrate argentaffin granules that are characteristic of monocytes and of most phagocytes.

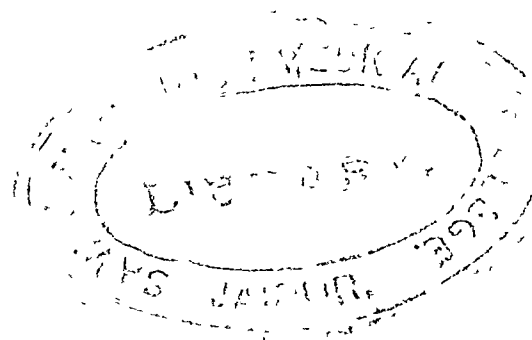


Primitive retothelial sarcoma arising in lymphoid tissue of tonsil. Its cells somewhat resemble monocytes and many of them are in mitosis.

PLATE II



Kodachrome photomicrograph of section of spleen in familial hemolytic jaundice. Note intense hyperemia of venous sinuses and small and insignificant splenic follicles. Small blue areas near center are trabeculae cut transversely.



or one node alone, rather than causing a generalized lymphadenopathy. Otherwise it is grossly indistinguishable from its fellows. Microscopically it is seen to comprise cells that are pyramidal and that anastomose with one another and often exhibit very bizarre forms. They are often multinucleated, and one frequently observes the formation of very large syncytial giant cells with many poorly formed vesicular nuclei. These sometimes exhibit atypical mitoses, and their tendency to phagocytose other smaller cells sets them off from megakaryocytes and aligns them with foreign body giant cells. Silver impregnation demonstrates reticular fibrils running among the cells and along their processes.

In this tumor there is again a resemblance to the pleomorphic lymphosarcoma and to the Hodgkin's sarcoma. Symmers believes that they are not retothelial sarcomas but pleomorphic lymphosarcomas with megakaryocytic giant cells. The explanation that any of these tumors of the lymphoid system as it becomes very immature and embryonal also becomes essentially mesenchymal seems to cover the matter satisfactorily.

Generalized Retothelial Tumors. It should be noted that the retothelial cell is not limited to the lymphoid apparatus, but may be found in areolar tissue under one of its aliases, "the histiocyte", it is not surprising, therefore, that these tumors may appear in tissues other than lymphoid in the organs and membranes of the body and in the subcutaneous tissue. Noncancerous forms have been reported as "reticulo-endotheliomatosis," with multiple small tumors composed of retothelial cells of good differentiation in various parts of the body occurring simultaneously. Sarcomatous tumors of the same origin have been reported, and we have seen them in our hospital.

Extramedullary Plasmocytoma. This growth has been excellently considered by Hellwig, who has reviewed the not too copious literature. It was mentioned in this book while we were considering medullary

plasmocytoma (see p. 143), from which it differs very little from the standpoint of microscopy, but very much from the standpoint of the clinician. It has a very uncertain ancestry, resemblance of its unit cells to plasma cells would imply lymphoblastic origin, and Hellwig somewhat diffidently assigns it to the lymphoblastoma family, where it has been arrayed in this book. On the other hand, it appears to avoid lymphoid tissue except in a certain region that of the accessory sinuses, tonsils, and upper respiratory passages. It may also appear on the eyelid. It presents two forms, malignant and nonmalignant.

Of 127 cases reviewed by Hellwig, 63 originated in the air passages, 47 in the conjunctiva, 4 in lymph nodes, and 13 in other organs. To this list Hellwig added one more, which he observed in the mouth, and another, occupying a tonsil, was reported in the same number of the Archives of Pathology, thus bringing the list of reported cases to 129, as of July 1943.

The growth affects men more often than women, the ratio is 5 to 1 for noncancerous and 13 to 1 for cancerous examples. In the case of conjunctival tumor, however, it is 1 to 1. The tumors may occur singly as non-invasive growths of the upper air passages and oral cavity, many of them originate from the turbinates or nasal septum, a few from the tonsils and fauces. Microscopically they appear to be composed of plasma cells, although some of them show a large admixture of lymphocytes. Nine of the collected cases cited above showed malignant characteristics. These differ from the solitary form only in being multiple. The age incidence is rather late, 40 to 82 years, or an average of 56.6. Ten of the collected tumors were locally invasive, and nine showed metastasis to the regional lymph nodes or to bone and the nodes. The microscopic appearance of the malignant tumors is not clear cut, they resemble plasmocytomas more or less and some of their cells may show distinct divergence from that cell with lymphocytic types admixed. On the

whole, these extramedullary plasmocytic tumors are not intensely malignant and differ sharply from the medullary form in their distribution and in the fact that they produce no urinary changes. It should be borne in mind, however, that they are occasionally very malignant.

Circulating Lymphoid Tumors (Lymphogenous Leukemia). Thus far we have been considering fixed tumors of the lymphoid organs. There are also two forms of circulating tumor which are known as acute and chronic lymphogenous leukemia. The chief site of the "growth" is the blood stream, and its cells are thrown into this from some or all of the sources of lymphocytes. The lymph nodes, the bone marrow, or the thymus or spleen may contribute.

LYMPHOBLASTIC LEUKEMIA (ACUTE LYMPHOGENOUS LEUKEMIA). Here the cells are of the immature lymphoblastic type. The disease occurs in young people and produces symptoms and a clinical picture not unlike that of myelogenous leukemia, running an acute course like that of the acute type of the latter. The lymphoblastic cells that characterize the microscopic picture look not unlike lymphoblasts, but they may be poorly formed and are regarded as a neoplastic variety of that cell; Furth and others have carried out experiments demonstrating that they are. In this form there is a very high leukocyte count and the percentage of lymphoblasts is much elevated; the latter appear more or less abnormal in smears and may exhibit mitotic figures. The histology of the enlarged lymph nodes is altered by an inundation of lymphoblasts, and the picture closely resembles that of lymphoblastic sarcoma; an inspection of the scanty blood vessels of the node will reveal large numbers of lymphoblastic cells in the blood. This is the most reliable criterion in the absence of blood smears or data thereon. The diagnosis is doubly difficult if there is an aleukemic phase of leukemia at the time of the biopsy, for then the blood is approximately normal and the nodes exhibit sarcomatoid changes. One need not face this

dilemma in myelogenous leukemia, where the cells are myeloid elements and hence foreign to the lymphoid tissue.

LYMPHOCYTIC LEUKEMIA (CHRONIC LYMPHOGENOUS LEUKEMIA). In this condition the cellular units are lymphocytes and the diagnosis is somewhat easier in so far as the pathology of the lymph nodes is concerned. There are large numbers of lymphocytes in the circulating blood, which may be of approximately normal appearance or may be of a size and type intermediate between the lymphoblast and the lymphocyte. The disease runs a slower course than does the lymphoblastic form and is therefore called "chronic." The lymph nodes become enlarged and sarcomatoid, and under the microscope they reveal a wiping out of their topography by myriads of lymphocytes that congregate in the sinuses, often in the form of aggregations or balls of cells that appear to be conglomerated and that probably represent foci of multiplication. Here again, the differentiation of leukemia, an aleukemic phase of this, and lymphocytic lymphosarcoma depends largely upon the blood picture, although the ball-like aggregations of lymphocytes in the sinuses are usually characteristic enough to turn one's suspicions toward leukemia rather than lymphosarcoma. Likewise, the presence of enormous numbers of discrete lymphocytes in the sinuses is of material aid in arriving at a decision.

PLASMA-CELL LEUKEMIA. This rare condition, which has been reported in a small number of cases, is referred to and dismissed in one paragraph of Wintrobe's excellent textbook on clinical hematology. There is a leukocytosis in the neighborhood of 60,000 cells per cu. mm., with anemia and symptoms of leukemia, the rise depending upon plasma cells, the origin of which is problematic. One case cited showed multiple medullary myelomas and another a plasmocytoma; in the rest of the cases studied there was no tumor to account for the plasmocytosis. After death such cases show infiltration of the bone marrow,

spleen, liver, and lymph nodes with plasma cells

LEUKOSARCOMA (LYMPHOSARCOMA CELL LEUKEMIA) Sternberg applied the term "leukosarcoma" to cases in which there was a leukemic blood picture in conjunction with lymphosarcoma. Isaacs has done considerable investigation on this condition. The cells in the circulating blood differ from ordinary lymphoblasts, having kidney shaped nuclei and a single prominent nucleolus which is more striking than that of an ordinary lymphoblast. The cytoplasm is deeply basophilic and scanty. Wintrobe states that fully half of the cases show a primary site in the anterior mediastinum, a case of lymphosarcoma of the thymus reported by Friedlander and the present writer probably represented one of these, as it showed an atypical lymphogenous leukemia with no involvement of the lymphoid tissue in general. A variety of primary sites have been reported, including the skin, retroperitoneal lymph nodes, and less likely origins. The disease may continue for months or years, but its leukemic phase is relatively short lived, covering from two days to two months.

MONOCYTIC LEUKEMIA There are leukemias in which the monocyte, derived from the retothelial system, plays the stellar role. It closely simulates leukemia from the clinical standpoint, but blood smears reveal large numbers of monocytes and "transitional cells" instead of granulocytes or lymphocytic forms. It probably has types very similar to those of lymphogenous leukemia and its allied disorders, in that it may show multiple retothelial sarcomas in association with it, or a form of "reticulosis," or histiocytosis similar to that to be discussed later as "Letterer-Siwe's disease." By some this is considered as an aleukemic phase of monocytic leukemia.

Prognosis of Various Forms of Lymphogenous Tumors One usually looks upon the dyscrasias in the lymphoid tissue which lead to malignant neoplasia with a great deal of pessimism, and this extends

to Hodgkin's disease as well. Naturally, if the tumors are multicentric and distributed over wide areas, surgery is out of the question, in the more localized examples a block dissection of the involved lymphatic chain can be carried out. The removal of single plasmacytomas, for instance, is successful in most instances, and lymphosarcomas of the alimentary tract are usually removable with a fairly good outlook for success. On the whole, however, treatment is a great problem. Lymphoid tumors respond to x irradiation like magic, but only a few of them respond with permanent cure. The plasmacytomas are more favorable. Hodgkin's disease will also respond very favorably, but from personal observation I know of but one ten year cure. The retothelial tumors appear to be slightly more amenable to this form of treatment. Gall and Mallory have worked out a scheme for prognosis, based upon the differentiation of the tumors observed in a series of over 600 cases, they feel that the better differentiated varieties run a slower course and hold out more promise of permanent cure by irradiation.

METABOLIC DISTURBANCES IN LYMPH NODES

These are the same as those which one observes in the case of the spleen, under which head (see below) they are discussed at length. They constitute various forms of histiocytosis and are readily confused with neoplastic changes in the nodes, so that they are of distinct importance.

THE SPLEEN

Even today this organ is still very poorly understood, its histologic composition indicates that it combines blood vascular and lymphoid elements to represent a sort of filter in the vascular bed of the body. Through phagocytosis and lysis it probably has much to do with the retirement of worn out corpuscles from the circulation and of particulate matter that may be formed therein. Certain it is that particulate matter deliberately injected into the veins of

animals promptly finds its way to the spleen and is engulfed by the phagocytes that abound there. If the spleen is removed other organs such as the lymph nodes, liver, and lungs will assume this function.

The normal spleen weighs about 115 Gm. It is a pulpy organ with a firm capsule and is bluish-red or slate-gray in color. It is convex on its latero-posterior aspects and concave mesially, where the splenic artery and veins have access to the organ. Seen at necropsy it is apt to be shriveled and flabby, but this is because most of its contained blood drains out into the abdominal circulation after death; if it is perfused under normal pressure (100 to 130 mm. Hg.) it takes on about one third again its size when first observed at the necropsy table.

This perfusion, when carried out with Ringer's solution, is a very necessary adjunct to subsequent fixation and sectioning for the study of the spleen's histology, as it washes out the "floating population" of hemal and other cells that obscure the architecture of its pulp. The trabeculae, partitions of a fenestrated sort, run into the organ from the fibrous capsule, dividing it up into a number of compartments. In these, in turn, course the large vessels from the hilum; in addition there are bundles of smooth muscle which, by their contraction, compress the organ and can empty it of much of its contents. For a while it was believed that this was noted only in the case of the lower animals, but an injection of epinephrine into the circulation of a human patient will be followed by marked contraction of the spleen, so that it can be considered to obtain in humans as well as lower animals. Furthermore, these contractions have been studied by leaving silver clips on the margin of the spleen (thus delineating its outline) and observing later with a fluoroscope and x-rays the contractions of these outlines as indicated by the shadows of the clips. Surgically, this is important, as the spleen may thus be emptied before splenectomy, reducing the

likelihood of hemorrhage and saving for the patient 100 cc. or more of useful blood.

After branching and leaving the trabeculae, the arteries penetrate the lymphoid follicles, where they form straight central axes and branch into other straight vessels which, because they are like the hairs of a paintbrush in the way they diverge, are called "penicilliary" arteries. These traverse small ovoid masses of lymphoid tissue, the ellipsoids, to terminate in conical dilatations like Erlenmeyer flasks, the ampullae of Thoma.

The veins begin as wide sinuses comprising a latticework of strap-like endothelial cells which show striations not unlike those of striated muscle (at a casual glance) and held together by hoops of reticulum. It has long been claimed that there is a membrane lining the sinuses that fills the interstices between the endothelial "staves," thus converting the sinuses into closed tubes. I have repeatedly attempted to demonstrate this membrane, using salts of silver which usually render isorefractile membranes visible, but to no avail. MacKenzie, Whipple, and Wintersteiner could never demonstrate it while working under far more "normal" conditions with transilluminated living mammalian spleens. The venous sinuses, as they grow larger, converge and become more conventional veins with a flat and continuous endothelium.

Between arterial and venous circulations lies a mass of spongy tissue with spaces filled with lymphoid and retothelial cells, the pulp spaces. It is supposed that there is a free communication between the arteries and veins: the blood leaving the ampullae through stomata, passing through the interstices in the pulp, and entering the venous sinuses through the gaps between the endothelial staves of their wall. The ampullae may communicate with the veins more directly, and it has been maintained that this closed circulation functions under ordinary conditions. When hyperemia supervenes, however, the arterioles proximal to the ampullae are supposed to become

pervious, transmitting blood to the pulp and thence to the sinuses and establishing an open circulation Whipple and his co-workers are sceptical concerning this mechanism In pathologic protocols of inexperienced men one sometimes reads that the venous sinuses are lined by a "swollen, cuboidal endothelium" This would be highly interesting if it were true, but the actual explanation is that the sinuses are lined by monocytic cells which are adhering to the specialized endothelium These may be washed out readily by perfusing the spleen with Ringer's solution, which when it emerges from the splenic vein will be found to contain leukocytes in large numbers, 75 per cent of these being monocytic

The other constituents of the spleen are the malpighian or splenic corpuscles which resemble lymphoid follicles in every respect and can be seen as tiny gray spots with the naked eye on the red, sectioned surface of the organ Anything inducing lymphoid hyperplasia enlarges these, while anything that produces overgrowth of the pulp or distends the venous sinuses tends to compress them and render them less conspicuous or almost invisible

In the discussion that follows amyloidosis, miliary tuberculosis, acute splenic tumor (swelling), and the like will be omitted, as they do not concern surgical pathology

Congenital Anomalies The spleen may occasionally fail to develop, or it may do so in the form of several small splenules which take its place, or there may be a normal spleen with one or several small accessory organs which may prove useful in making frozen section diagnosis, as they show the same changes as those present in the larger spleen and may thus be instrumental in averting an impending splenectomy by revealing nothing of a pathologic nature

Trauma Traumatic lesions are not uncommon, particularly gunshot wounds, but they do not call for surgical pathologic diagnosis As a result of damage to hilar vessels,

or through the dissolution of infarcted areas, large blood cysts may develop in the organ

Cysts Splenic cysts are rare, only 148 having been reported up to 1941, according to McClure and Altmeier These authors classify splenic cysts very much as did Fowler in a classic paper of 1913 They recognize two broad varieties true and false Of the former there are two groups epithelial, including dermoid and epidermoid cysts, and endothelial, which comprise cavernous hemangiomas and lymphangiomas (not really cysts) and polycystic disease, together with some serous cysts Polycystic disease is somewhat analogous with polycystic disease of the liver and kidney and is congenital Added to this are hydatid cysts, caused by the echinococcus Under the heading of "false cysts" these authors include hemorrhagic, serous, inflammatory, and those attributable to liquefaction of infarcts, which have been mentioned under "Trauma" (above)

Some of these cysts may undergo calcification of their walls These are usually unilocular, and their etiology is largely a matter of conjecture We have one in our collection that measures 15 x 8 x 8 cm, is almost like an infant's skull in its appearance, was filled with grumous brown material when removed (obviously hemorrhagic debris), and gave no symptoms prior to removal Like many of these, it was discovered on an x-ray film taken in the course of a physical examination by an insurance company

Splenomegaly This term, meaning "largeness of the spleen," includes a number of conditions that have widely diverging etiology In malarial districts the malarial spleen or "ague cake" is so common as to make this the most usual cause of splenomegaly In Banti's syndrome the spleen is enlarged because of interference with the portal circulation In Gaucher's disease the etiology is quite obscure The leukemias produce enormous spleens on occasions, particularly the myelogenous type

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Hemolytic jaundice also produces splenomegaly.

BANTI'S SYNDROME. The spleen may be affected by a number of vascular disturbances, chronic passive congestion being the commonest, but we are concerned here with only a few. Of these that noted in Banti's syndrome is of prime surgical importance.

Originally Banti believed that this was a specific infection which caused enlargement



Section of spleen from case of Banti's syndrome. Note conspicuous and generalized fibrosis and gaping, stiff-walled sinuses. Few follicles are to be seen.

of the spleen until it weighed from 400 to 800 Gm. Now it is considered as a syndrome which depends chiefly upon interference with the outflow of venous blood from the organ. This may be due to intrinsic reasons, such as phlebitis of the splenic vein with thrombosis, or to pressure on this vein at the hilum of the spleen, or to other extrinsic factors involving obstruction of the splenic vein as it courses over the pancreas. Or it may be attributable to portal obstruction outside of the liver or within its substance.

In the first case typical factors would be pylephlebitis and thrombosis or (less frequently) a spread of the normal obliterative fibrosis of the umbilical vein through the left branch of the portal and into the portal vein, whereby it would become obstructed. This has been noted by Allen Whipple in

several instances. The obstruction within the liver is usually part of a portal cirrhosis. Thus the portal obstruction backs up the circulation in the spleen, where it occasions stasis and fibrosis. With this one usually observes esophageal varices, which are discussed elsewhere in this book (see p. 213). The spleen becomes enlarged, its capsule fibrous and thick; if thrombosis has been a factor it will usually be accompanied by areas of splenic infarction. As a result of the stasis the splenic reticulum becomes very much thickened and overgrown; as the process continues it becomes converted into collagenous tissue. Similar reticular changes are noted in connection with rickets, but these do not go on to the formation of collagen.

HEMOLYTIC JAUNDICE. In this disease the spleen attains considerable proportions, and in most instances its removal occasions remarkable improvement. Two forms are described: the congenital familial type of Minkowski and the acquired type of Hayem and Vidal. The first is much the commoner. As Boyd points out, the term "congenital" does not always apply, as the disease may develop after birth, but it is definitely familial in its incidence. There is acholuric jaundice with enlargement of the spleen and an anemia of the normocytic group that is characterized by spherocytosis in which the red corpuscles swell into a spherical shape and lose their normal flexibility. In the acquired form acute exacerbations of fever, malaise, and intensified jaundice, together with splenomegaly, are typical.

Gross examination of the spleen from patients with hemolytic jaundice reveals an organ that is enlarged four or five times and weighs on the average 1 Kg. The capsule is tense and the parenchyma firm and bloody; over the capsular surface there may be shaggy adhesions between the spleen and diaphragm. Section shows a dark red surface that is the color of porphyry or beefsteak, drips blood, and is traversed by delicate whitish lines corresponding to the trabeculae. The follicles are not visible.

The microscopic appearance of sections is quite characteristic, although it presents nothing academically specific, the pulp is tremendously engorged, while the venous sinuses may be empty or may show similar hyperemia Whipple explains the engorgement on the basis of the spherocytosis, which makes the bulky corpuscles unwieldy and causes them to become congested in the vascular channels, but more particularly those of the pulp They are like a crowd of obese people at a reception On account of the engorgement of the pulp and venous sinuses the corpuscles become compressed and may become very small and insignificant A variable number of macrophages containing hemosiderin may be found clustered in the trabeculae or pulp, or hematin crystals may be observed lying free among the erythrocytes This attests to the hemolysis that has been taking place Phagocytosis of erythrocytes by macrophages may be noted, but it is usually very inconspicuous The general appearance of the organ, then, is one of intense engorgement without any striking reaction to this Infarcts and fibrosis are lacking

THROMBOCYTOPENIC PURPURA In this disease the spleen may also become enlarged, and in its chronic form splenectomy often results in marked amelioration of the symptoms Aside from this enlargement any pathognomonic signs have yet to be demonstrated The marked purpuric symptoms and the anemia that accompanies them lead one to expect something definite in the pathology of the spleen, but one is usually disappointed It has been said that the phagocytosis of platelets may be observed, but usually there is not sufficient increase in the number of macrophages to encourage one to carry out special methods for demonstrating the platelets, which are not clearly visible in ordinary methods of staining and require special fixation The reader is referred to papers dealing with this subject suffice it to say that for any practical purposes the pathologic characteristics of any

histologic change in the spleen are entirely lacking

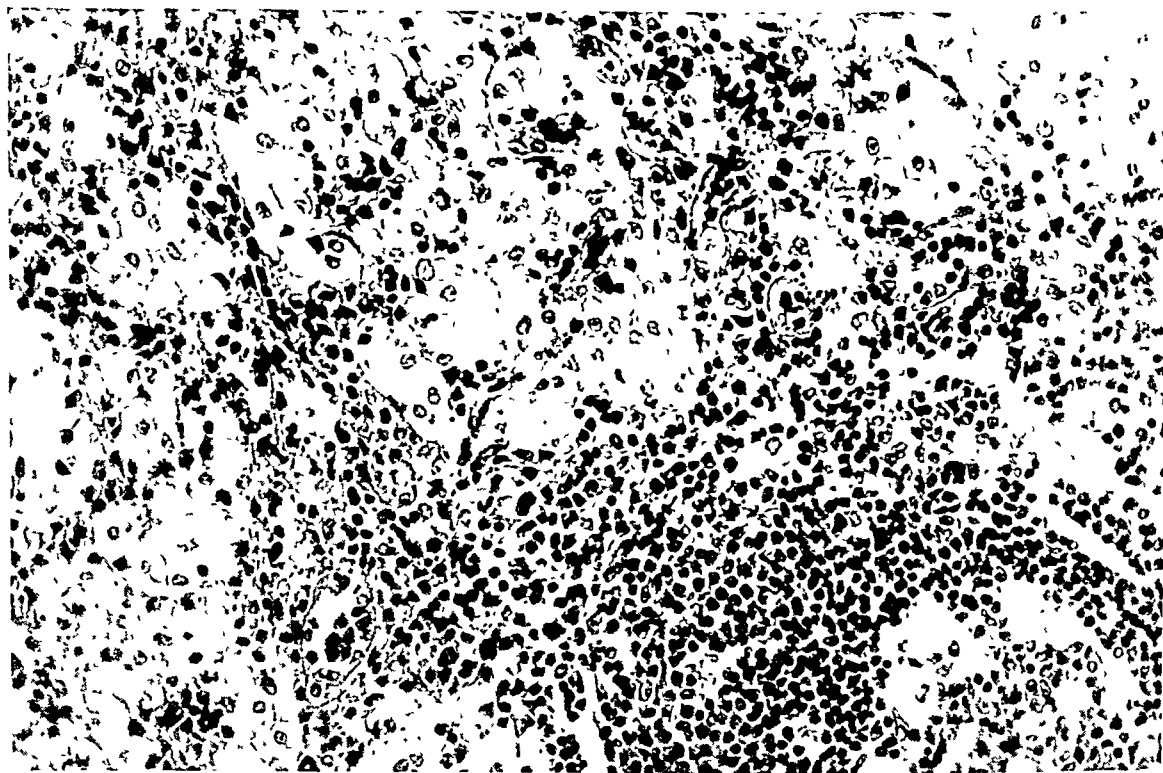
GAUCHER'S DISEASE Probably the most striking metabolic disease, in so far as the spleen is concerned, is Gaucher's splenomegaly, in which the organ may become so enormous that it reaches from diaphragm to pelvis and has attained a recorded weight of 8,100 Gm There are practically no symptoms aside from pruritus, and the physical signs are limited, the enormous spleen is palpable, there may be an increasing pigmentation of the skin, and the eyes may reveal pigmented pingueculae over the outer aspects of the globi These, when present, are very characteristic The disease develops insidiously in childhood and may persist through life, indeed a 20 year history is not uncommon In spite of the greatly enlarged spleen women have successfully borne children while suffering from Gaucher's disease The spleen is bluish gray to brownish, and its capsule may show shaggy adhesions which are more or less common in any variety of splenomegaly On section the pulp is grayish and somewhat translucent, the follicles are practically invisible, owing to lack of contrasting background

Microscopic pictures are dramatically typical, the pulp and sinuses are flooded with large cells resembling melon seeds in their outline and traversed by delicate striae that represent partitions between elongated vacuoles These contain a light yellowish pigment, the nature of which has long been under discussion without any definite solution having been reached as to its chemical nature, it is weakly iron positive The familiar stains for fats will not demonstrate any lipids, the substance contained in the vacuoles being cerasin (a cerebroside first identified in 1924 by Epstein and Lieb), which shows no affinity for these dyes Aside from the presence of these strange cells in the meshes of the pulp and, to a lesser degree, in the sinuses, there is little pathologic change in the histology of the organ unless it be the inevitable generalized fibrosis that accompanies its in

crease in size. The nature of the Gaucher cells is not too well understood; they are usually considered to be macrophages.

This disease is not limited to the spleen; similar lesions are noted in the retothelial tissue in general, so that Gaucher's cells may be found in the lymph nodes, the bone marrow, the sinusoids of the liver, and (very

phages that contain spherical, not elliptical, vacuoles filled with a lipid that stains positively with sudan dyes and Nile-blue sulfate and has been identified as sphingomyelin. The lesions of the disease are even more widely disseminated in the body than are those of Gaucher's disease, and the lipid-bearing cells circulate freely in the blood,



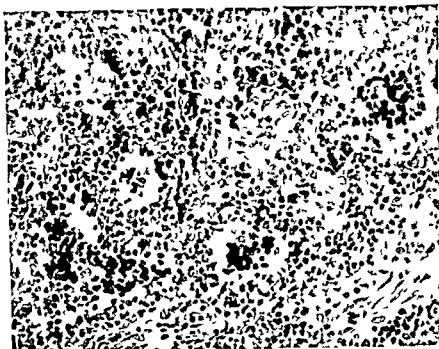
Part of a splenic follicle in Gaucher's disease. Large "melon-seed cells" are everywhere and are invading the lymphoid tissue of this follicle. (Compare them with similar cells in the picture of one of the splenic types of Cooley's anemia.)

occasionally) in the circulating blood. This may also show a moderate anemia of a normocytic type, and monocytosis may occur. The lipids of the blood vary within normal limits. The disease is said to have a predilection for Jews.

NIEMANN-PICK'S DISEASE. This is also a systemic disease that is even more frequently noted in Jews than is Gaucher's disease. It is observed only in infancy. The spleen is enlarged, though not so much as in Gaucher's disease, and its removal produces results that are at best temporary, for the patient dies after a few months' illness. The splenic picture is similar to that of Gaucher's splenomegaly, excepting that the large cells are more obviously macro-

where they may be identified in smears. The blood cholesterol may be elevated.

XANTHOMATOSIS (Hand-Schüller-Christian's Disease). The lesions of this disorder are still more widespread than those just described. Not only are the spleen and lymphoid organs involved, with the bone marrow and liver, but lesions also occur in the bones, particularly those of the skull; these may be mistaken for myeloma. The lipid-bearing cells are apt to be smaller than they are in the other histiocytoses and to resemble the foam cells of xanthoma, or "Touton cells." In the beginning these cells contain granules which enlarge and become droplets of cholesterol. Aside from containing the characteristic cells the spleen may



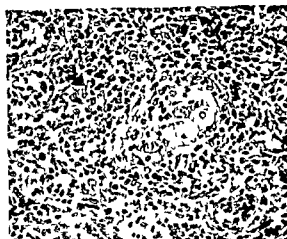
Spleen in Cooley's Mediterranean anemia, showing hemopoietic type of lesion with immature hemic cells grouped as islands in the widely dilated venous sinuses

not be prominently altered, nor is it greatly enlarged, other organs such as the bones may show more conspicuous lesions. The disease is not familial.

The clinical aspects of xanthomatosis were first well described by Rowland in 1928. There are symptoms of irritability, polydipsia, polyuria, swelling of the gums, and loosening of the teeth. There are eroded defects in the flat bones, those of the skull being very prominent on x-ray examination. Exophthalmos is present. Thus, the differential diagnosis of this condition is relatively simple on a clinical basis, and biopsies are seldom taken.

MEDITERRANEAN (COOLEY'S) ANEMIA
This disease has already been mentioned under the heading of anemia, but as it presents splenomegaly mention of it is properly included here. The spleen becomes very much enlarged, almost as much so as in Gaucher's disease, and it is reddish, but otherwise not strikingly characteristic. Two types of histologic picture may be noted microscopically, though the reason for their difference is not clear. The spleen may show

marked myeloid activity, with islands of hemopoiesis and immature blood cells grouped into masses that resemble marrow, or the picture may resemble that of Gaucher's disease sufficiently to be mistaken for it. In the latter instance there are many



Spleen in Cooley's Mediterranean anemia, showing type which simulates Gaucher's splenomegaly in its histology. At center is group of "melon seed cells" almost if not quite identical with those of Gaucher's disease in their appearance

large cells that are indistinguishable morphologically from the Gaucher cells. Transitions between the two pictures may be noted, with combined hemopoiesis and the presence of large vacuolated cells occurring simultaneously. The clinical features of the disease are so striking that biopsies are seldom necessary; splenectomy is occasionally performed, but has not yielded very promising results.

LOCALIZED AGNOTOGENIC XANTHOMATOSIS OF THE SPLEEN. Dreyfuss and Fishberg have recently described a case of splenomegaly that fails to fit into any of the categories just considered. Their patient exhibited a spleen that was enlarged three diameters, showed a few fibrous adhesions, and was of a dull brick-red with numerous grayish miliary nodules on the sectioned surface. Microscopically the pulp was found crowded with large foam cells that did not invade the sinuses. Chemical analysis of the organ revealed an increase in all the lipoids, particularly lecithin and cephalin. Thus there were chemical features that warrant including the paragraphs on this new form of histiocytosis at this point. The authors include a useful table in their article which is appended to a classification of the lipoidoses and reproduced here.

- A. Cerebroside lipoidosis: Gaucher's disease.
- B. Phosphatide lipoidosis: (I) Niemann-Pick's disease; (II) amaurotic idiocy or Tay-Sachs' disease.
- C. Xanthomatosis or cholesterol lipoidosis: (I) Idiopathic: (a) acute: Letterer-Siwe's disease; (b) chronic: (1) Hand-Schüller-Christian's syndrome

and (2) generalized forms; (II) secondary xanthomatoses.

The tabulation of the lipid content of the spleen in these lipoidoses, compared with normal limits, may prove to be useful. It is given at the foot of this page. The lipoids are expressed in figures representing mg. per 100 Gm. dry weight.

LETTERER-SIWE'S DISEASE (NONLIPOID HISTIOCYTOSIS). This disease has been known for some time under a number of names; those that might be listed in addition to the two given above are reticulosis, reticulo-endotheliosis, and aleukemic monocytic leukemia. In it there is marked enlargement of the spleen, together with ill-defined symptoms pointing toward some sort of purpura, with hemorrhagic dermal lesions and anemia. The retothelial system shows signs of generalized stimulation, and in one group of cases there is evidence to show that the disease is indeed a form of monocytic leukemia in an aleukemic phase. In another group of cases, however, there is nothing that points definitely to this, and most of the patients in this group give a history of repeated colds, sore throat, and similar apparently insignificant symptoms. The liver is usually enlarged, but the spleen is more strikingly so, being two or three times its normal size. Its sectioned surface exhibits pearly gray areas about 3 mm. in diameter, but otherwise it is not conspicuously changed in appearance. The microscope shows it to be somewhat sclerotic, with thickening of the fibrous tissue in the trabeculae and capsule. The pulp and sinuses are thronged by large polyhedral cells with a dense, rather than vacuolated, cytoplasm. Their nuclei may be multiple,

	Normal	Niemann-Pick	Gaucher	Tay-Sachs	Dreyfuss-Fishberg
Total cholesterol. .	0.6- 2.3	6.73	2.72	2.67	6.36
Free cholesterol. .	0.5- 1.1	6.70	0.52	1.00	3.12
Cholesterol ester .	0.2- 1.2	0.03	2.20	1.67	2.20
Total phospholipids.	5.5-11.0	42.50	9.39	6.58	18.30
Lecithin . .	3.1- 4.0	.	7.34	4.44	10.24
Cephalin .	1.6- 4.0	.	1.50	1.23	7.11
Sphingomyelin ..	0.7- 1.1	32.70	0.55	0.91	0.95
Cerebrosides	Traces		6.65	.	Traces

or lobulated and of the gigantic type. These cells are smaller than those of Gaucher's disease or of the other xanthomatous maladies just described, and they show no evidence of any lipid content or of cerasin. Many of them are found to be phagocytosing erythrocytes, in short, they appear to be macrophages. As in the splenomegalies we have just discussed there is a tendency for the involvement of the entire retothelial system, the lymph nodes, the marrow, and the sinusoids of the liver all show the typical cells.

Inflammation Infectious Granuloma TUBERCULOSIS Because the acute forms of inflammation are not our concern here we omit the acute inflammatory conditions such as "acute splenic tumor" or "acute splenitis," as well as infected infarcts, and proceed with the more chronic lesions. Splenic tuberculosis, for that matter, is important to the surgical pathologist only when it is discovered by accident in a spleen removed for the treatment of some other condition. This is not too uncommon a finding, and it should be recognized. It is usually found to be well advanced, and it presents a picture of scattered conglomerate tubercles which may or may not be recognized on gross examination and which cause a good deal of surprise when discovered under the microscope. Tuberculosis of lymph nodes at the hilum of the organ may cause pressure upon the splenic vein and bring about Banti's syndrome, with the production of a large fibrosed organ that may show infarcts.

BOECK'S SARCOID This may produce marked enlargement of the spleen, up to 750 Gm or so. The organ is red, its capsule thick, and its sectioned surface beefy, with rather prominent yellowish white dots that suggest submiliary tubercles. Microscopically, however, these show the characteristic fibrous and noncaseating structure of the 'sarcoids' (which has already been described in the section on lymph nodes). The lymph nodes, as in tuberculosis, may

share in the process and exhibit similar lesions.

SYPHILIS This, of course, may affect the spleen, but aside from causing very characteristic lesions in the "flinty" spleen of infants with congenital lues (an organ fairly crawling with *Treponemata*) it is not apt to show anything strikingly different from luetic lesions anywhere. There may be marked fibrosis, rarely very fibrous gummas may be observed.

MYELOSIS If the bone marrow is interfered with in such a way as to prevent hemopoiesis, the spleen often takes over that function, becoming enlarged but not much altered in its gross appearance. The microscopic picture, however, is striking, there are areas of myeloid cells of an immature type, many of them resembling (and representing) hemocytoblasts and grouping into well defined blood islands. Megakaryocytes are so readily recognized that they are probably the first sign to call one's attention to the myelosis. They are scattered at random through the pulp. Such a condition usually follows acute infectious illnesses in children (it is often noted after diphtheria and scarlatina) or it may result from invasion and replacement of the marrow by metastatic tumor. It may reach a degree so striking that the pathologist will suspect myelogenous leukemia or believe that he is dealing with an aleukemic phase of this. In such cases examination of the bone marrow, together with the clinical history and findings in blood smears, will set him right and aid him in coming to a conclusion.

MYELOGENOUS LEUKEMIA Since myelosis has been mentioned it would be best to go on to a brief consideration of myelogenous leukemia which may involve the spleen to so marked a degree as to produce enlargement of the organ that rivals that noted in Gaucher's splenomegaly. While the spleen may be but little enlarged in acute myelogenous leukemia, weighing in the neighborhood of 600 Gm, in the chronic form of the disease it is usually about 1,800 Gm in

weight, and it has attained as much as 10 Kg. Its capsule may be thin, but usually it is thickened and opaque; its sectioned surface is a characteristic gray or yellowish-gray and shows very little in the way of topography. Microscopically the entire organ is converted into a mass of myeloid tissue which is chiefly composed of immature cells of the white or granulocytic series. We have spoken earlier (p. 145) of the greenish tumors which may be found in connection with myelogenous leukemia, in the form known as "chloroma." The microscope will show that the cellular types that predominate in the section will correspond with those found in smears of blood: myeloblasts in the acute form, myelocytes in the chronic. If the latter be the eosinophilic type one will naturally find that most of the cells are eosinophil myelocytes and leukocytes. One should distinguish between acute myelogenous and acute lymphogenous leukemia, which have a close superficial resemblance. The diagnosis depends largely upon the examination of smears of the patient's blood which have been treated for the peroxidase reaction; when it is positive lymphogenous leukemia is ruled out. Monocytic leukemia may also be troublesome in this respect, and the peroxidase reaction is positive in that disease, but the granules are fewer and finer, some cells showing none. Peroxidase reactions on sections are difficult to carry out and not as satisfactory as they are on blood smears.

Tumors of Spleen. Although in some animals (old dogs, for example) this organ is a frequent site of tumors, it is almost notoriously free from them in the human subject. With the exception of malignant melanomas, pulmonary carcinomas, and a few other carcinomas with very widespread metastatic distribution, very few tumors metastasize to the spleen. For this reason there has long been a superstition that the spleen may secrete an antineoplastic substance.

So far as primary tumors are concerned, if we consider the histology of the spleen

we will find that there is little else but vascular, lymphoid, reticular, and fibrous supportive tissue, with a slight admixture of smooth muscle in the trabeculae. Any of these might constitute a starting point for primary tumors, but the vascular and reticulo-endothelial elements are the only ones to do this with any regularity, and they do not do it often.

VASCULAR NEOPLASMS. The commonest of these is the cavernous hemangioma, but in twelve years we have seen but two in our hospital. They resemble cavernous hemangiomas elsewhere in the body, enlarging the spleen or bulging from its surface; the spleen in that case perches like a small, firm cap on the surface of the tumor. If their connection is with the arterial system they will produce abdominal bruits in the left upper quadrant. They tend to undergo extensive thrombosis which wipes out their microscopic architecture to an extent where orientation is difficult. Occasionally malignant varieties have been reported, with metastasis to the liver, presumably along the portal system.

RETOTHELIAL TUMORS. Reticulomas, as we have seen, are as yet to be recognized, but retothelial or reticulum-cell sarcomas have been fairly frequently reported, particularly during the past few decades. They are tumors which grow diffusely in the organ, enlarging it and presenting the microscopic characteristics of retothelial sarcoma. They, too, metastasize to the liver.

LYMPHOID TUMORS. Any widespread lymphosarcoma may involve the splenic follicles, or such a sarcoma may have origin in one or more of them. Hodgkin's disease may sometimes begin in the spleen ("splenic Hodgkin's") and give rise to an unrecognized splenomegaly for a year or two before the diagnosis is made by its appearing elsewhere, often in the spinal canal.

FIBROUS TUMORS. Fibroma and fibrosarcoma could readily begin in the capsule or trabeculae, but they are very rarely noted or reported.

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Respiratory System and Mediastinum

NOSE

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NOSE

Operations upon the nose produce chiefly surgical specimens that have been the cause of mechanical obstruction to the nares, or biopsies from such structures. Naturally there are exceptions, but the otorhinologists and laryngologists treat only certain types of disease and are the chief contributors of surgical specimens from the ear, nose, and throat. There is little reason, therefore, for systematically considering all the malformations and inflammations that might be found in these organs. It should be understood that we are concerned with the usual run of material that comes to the laboratory from the services concerned with diseases of the ear, nose, and throat. The pathologist seldom sees the patients and seldom receives a specimen that has not been more or less comminuted by the necessity for removing it through a narrow passage. These specimens usually represent hypertrophied turbinate bones, fragments of deviated septa, polyps, and the like, with a scattering of biopsies from suspected cancerous lesions. Sheets of hypertrophic mucosa from antra or sinuses such as the ethmoid,

fragments of mucosa and bone from Caldwell-Luc operations, and a copious supply of tonsils and adenoid tissue make up the rest of the material.

INFLAMMATION **HYPERPLASIA OF MUCOSA** This is seen in a number of inflammations of the nasal passages. In its acute form it is left severely alone, but in cases that have become chronic the mucosa is often stripped from its bed. It exhibits very little on gross inspection, but under the microscope it falls into two chief classes: hyperplasia of the mucous glands with banal chronic inflammation, and subacute inflammation of the submucosa with large numbers of eosinophil leukocytes attesting to an allergic reaction. The latter is very frequently obtained from patients with hay fever, bronchial asthma, or other allergic conditions. In both types there are possibly a few neutrophil leukocytes and many lymphocytes and plasma cells that may be degenerating and forming Russell bodies in large numbers. Hyperemia and edema are common to both forms.

NASAL POLYPS ("ALLERGIC POLYPS") Hyperplasia and chronic inflammation of the nasal mucosa and that of the accessory sinuses may go on to the production of soft, translucent, polypoid masses of ma-

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lesions. These must be differentiated from tuberculosis by the usual morphologic criteria; they tend to show more lymphocytes than epithelioid cells, giant cells are not so numerous, necrosis is of the gummatous and not of the caseous type, and vascular lesions, with angitis and prolifera-



Area from adenoma of antrum of Highmore. This is a true papilloma and is to be distinguished from the commoner "nasal polyp," which is a granuloma. Note compound columnar epithelium.

tion of the vascular endothelium, are apt to be strikingly noticeable.

Nonmalignant Tumors. *Adenoma.* This polyp, a true adenoma, shows marked overgrowth of glandular tissue of the submucosa, and is firmer, more globular, and covered with hyperplastic mucosa. Microscopically there is confirmation of the glandular overgrowth, and evidence of a superimposed chronic inflammation is very likely to be found.

Fibroma. There are two types of this in the literature, the "soft" and the "hard," but the former is seldom a true soft fibroma, as it will be found to be merely an allergic

polyp, which has already been described. The hard fibroma, which usually occurs in young patients, grows out from the antrum into the nares, filling them almost completely. This is the "juvenile fibroma of the nares." Microscopically it is found to be much more fibrous and substantial and less edematous than are the allergic polyps.

Angioma. There is always a possibility of angioma occurring in the nose, particularly the sclerosing type that is characterized by the overgrowth of the adventitial histiocytes. These tumors have been made a special topic for discussion by Orslos, who has called them "Gemmangiomas" (See chapter on Cardiovascular System). If there is a possibility of encountering angioma, there is always a lesser one of finding malignant varieties of that tumor.

Other Tumors. Being surrounded by bone and cartilage and separated into two compartments by a partition composed of the same tissues, the nose would appear to be good ground for the growth of chondroma or osteoma or their malignant varieties. This is not the case, however, as they are rarely seen. Tumors may originate in the nerves of the nares and pharynx, and very occasionally meningiomas that arise near the olfactory bulbs may penetrate the cribriform plate of the ethmoid bone and appear in the nares, where they may afford considerable puzzlement upon microscopic examination. The only one personally observed was malignant and fatal, but this is not necessarily true of all of them. Plasmacytoma of the extramedullary type may arise in the nose and nasopharynx, this has been fully discussed in connection with the lymphoid tissue.

Malignant Tumors. *Carcinoma.* It is generally conceded that there are three types of nasopharyngeal carcinoma: cylindrical, squamous (epidermoid), and undifferentiated. The first two of these are fairly uniform and run true to type, the third group is less satisfactory as regards classification. The cylindrical celled tumor is an adenocarcinoma originating in one

terial that is yellowish and resembles inspissated mucopus at first glance. These are in no sense tumors but represent a chronic inflammation of the submucosal connective tissue accompanied by marked edema and an infiltrate that usually exhibits large numbers of eosinophils. The polyps are from 1 to 3 cm. in length and



Allergic type of nasal polyp. This is covered by normal respiratory epithelium, contains two mucous glands, and is otherwise composed of gelatinous, edematous connective tissue containing eosinophils in large numbers.

about 7 to 10 mm. in diameter. The microscope reveals an insubstantial-looking mass of edematous connective tissue infiltrated by myriads of eosinophils, plasma cells, and lymphocytes. Dotted about, like islands in a flood, are mucous glands with their ducts leading to a surface that is covered by a rather simple columnar mucosa that may be ciliated and usually is of the stratified columnar type. This may show small areas of ulceration and more acute inflammation. Bacterial stains are usually disappointing, as they reveal only a superficial infection. Micrococci predominate, but it is difficult to identify them, and if the surgeon desires

a bacteriologic diagnosis he should be referred to the bacteriologist, or cultures should be taken and the organisms studied and identified according to the precepts of bacteriology.

TUBERCULOSIS. This may take three forms in the nose: lupus vulgaris, as an extension from the skin; tuberculous polyps; or tuberculous ulcers.

Lupus. This is a diffuse process on the surface of the mucosa which causes thickening and reddening, together with signs and symptoms of chronic inflammation. A biopsy will show a microscopic picture of scattered tubercles in the submucosa that is similar to that seen in cutaneous lesions of lupus.

Tuberculous Polyps. These differ from the "allergic polyps" in that they are firm, globular, yellowish-brown, and opaque. Small yellowish tubercles may be discerned on the sectioned surface, but usually they are too small to be identified with certainty. The microscope reveals somewhat fibrous hyperplastic submucosa containing typical tubercles that may be miliary or conglomerate. Caseation may be present in older examples, but it may be replaced by a more fibrous form of tubercle. If the examiner is patient, sections stained with carbol-fuchsin will usually reveal a few bacilli in the epithelioid or in the giant cells.

Tuberculous Ulcers. These appear most frequently in the nasopharynx of sufferers from pulmonary tuberculosis. They are shallow, indolent, and reddish-gray; the microscope will reveal tubercles dotted about the granulation tissue that covers their beds and in the thickened tissue at the margin of the lesions.

SYPHILIS. The so-called "saddle-nose" deformity of syphilis is familiar enough to require no special mention beyond the statement that there may be extensive destruction of the nasal tissue, including the bone. More important from our standpoint are the gummatous lesions which develop rapidly in the mucosa, submucosa, periosteum, and bone and tend to cause early sloughing

PHARYNGEAL VAULT

There is little of a pathologic nature in this situation save the "adenoids" (discussed with the tonsils) and the tumors harbored by this recess behind the nares. It not only produces lympho epithelioma, but on account of the origin of Rathke's pouch in this situation those tumors which have been described as arising from this structure will also be found here. These are essentially teratomas and chiefly produce epidermoid tissue, which may form dermoid cysts and sacs filled with sebaceous material, or they may produce bone, cartilage, or abortive ameloblastic structures. One frequently finds that most such tumors are made up of the tissue of the enamel organ (These "craniopharyngiomas" are discussed elsewhere in connection with the hypophysis.)

Chordoma This neoplasm, which takes origin from the remnants of the embryonal notochord, has been discussed in connection with the connective tissue tumors. Chordomas may arise at the base of the skull and penetrate into the vault of the pharynx, invading its walls extensively.

LARYNX

The surgical pathology of the larynx is largely restricted to the study of small samples of tissue removed in the otolaryngologic clinic, usually with a view to ruling out a diagnosis of cancer. Occasionally biopsies are taken from inflammatory lesions for a specific diagnosis.

Inflammation Chronic inflammation is often encountered in biopsies from the larynx. There are edema and thickening and fibrosis of the tissue in and about the vocal cords, and the biopsies reveal very little to the unaided eye. Microscopically they exhibit evidence of the gross peculiarities just enumerated and of a lymphocytic infiltration which may or may not be follicular in its distribution. Tuberculous lesions are usually ulcerative and may be investigated by taking biopsies from them. Under the

microscope these will show typical tubercles, but to the naked eye they are merely small bits of tissue, usually already fixed in formalin. The disease may be superficial and ulcerative or infiltrating and fibrous.

LEUKOPLAKIA A very common outcome of chronic inflammation or overuse is leukoplakia, which consists of focal thickening of the epidermal epithelium, loosening and edema of its squamous layer, and down growth of its rete cones into the stroma, without any evidence of malignant characteristics. This distinguishes it from epidermoid carcinoma. The lesion is often spoken of as a "laryngeal corn" on account of its resemblance to a calvus on the skin.

Tumors FIBROMA This is often called a "singer's node," as it is found most frequently in the larynges of singers, public speakers, and hucksters. Obviously this connection with inflammation and overuse makes it questionable whether this condition should be arrayed with the neoplasms or considered as a focal fibrosis due to chronic inflammation. It is a small fibrous node a few millimeters in diameter which is composed of rather dense collagenous fibrous tissue, sharply delimited and microscopically characterized by a lack of cellular elements and a great quantity of collagenous fibers.

CHONDROMA Small chondromas develop in and about the vocal cords from the cartilaginous tissue that constitutes the bulk of the larynx.

PAPILLOMA Very occasionally one encounters small papillary tumors that are in every respect analogous to the epidermoid papillomas of the skin or epidermoid mucous membranes.

Malignant Tumors CARCINOMA When this arises orad to the vocal cords this may be of the epidermoid type, when it is found below them it may be of a type resembling the Schneiderian carcinomas of the nasopharynx. Adenocarcinoma may be produced by the mucous glands in the neighborhood of the mucosa, arising in one vocal cord and spreading slowly along it until the

part or another of the glandular epithelium of the nose and its accessory sinuses. Epidermoid carcinoma usually develops from those parts of the nasal cavities already covered by epidermal membrane. The third group includes tumors which Ewing believed to arise in the respiratory ciliated epithelium (Schneiderian membrane) of the nasal passages. Macroscopically they are unremarkable. Their microscopic picture, however, is often puzzling. They grow in sheets or masses of cells, or form abortive glandular structures; some of the small-celled varieties are reminiscent of neuro-epithelioma and may form abortive rosettes. There are also atypical adenocarcinomas that arise near the base of the nasal septum and have been attributed to the somewhat mythical "Jacobson's organ," an embryologic structure that apparently fails to persist in the human subject. All these are problematic tumors that may best be left in an "undifferentiated" group until they are more closely identified.

LYMPHO-EPITHELIOMA. This is described elsewhere with the lymphoid tissue and the alimentary tract. It is often found in the floor of the nasal cavity and in the nasopharynx. Its incidence in this situation appears to be unusually common in China.

Grossly it forms soft white masses in the mucosa and beneath it.

Tabulation of Nasal Tumors. Ewing's tabulation of tumors of the nasal passages and paranasal sinuses may be found useful and hence is given at the foot of this page.

Most of these conditions have been covered elsewhere in this book. Angiomyxomas are tumors composed of a nexus of vessels surrounded by myxomatous tissue. They are included by Orsós among his "gemmangiomas," as he believes that the adventitial cells of these vessels undergo mucoid degeneration. His article illustrates some very beautiful examples. Ewing's inclusion among these of rhinoscleroma and empyema of the antrum is rather surprising.

PARANASAL SINUSES

The foregoing pages apply also in the main to the antra and sinuses. The maxillary antra are very near the teeth of the upper jaw, so infection from these may spread into the antrum, and tumors that are peculiar to the alveolar processes of the maxilla are also apt to invade these cavities. Carcinoma may originate in the antral mucosa and exhibit an adenomatous type of growth.

EWING'S TABULATION OF NASAL TUMORS

<i>Nares:</i>	Polyps:	Mucous, myxomatous, fibromatous, angiomatous. Choanal angioma, angiomyxoma, myxosarcoma. Juvenile fibroma. Epithelial papilloma.
	Mucosa:	Schneiderian adenoma, adenocarcinoma, carcinoma. Lympho-epithelioma, squamous carcinoma, melanoma. Lymphosarcoma, plasmocytoma, rhinoscleroma.
<i>Antrum.</i>	Mucosa:	Cysts, empyema, cystic myxoma, fibroma.
	Bones:	Osteoma, fibro-osteoma, chondroma, giant-cell tumor, endothelioma.
	Teeth:	Dental cysts, odontoma, adamantinoma
<i>Ethmoid:</i>		Fibroma, osteoma, carcinoma, meningioma, ganglioneuroma.
<i>Sphenoidal Sinus:</i>		Polypoid myxoma, carcinoma.
<i>Frontal Sinus:</i>		Osteoma, adenoma, carcinoma.
<i>Pharyngeal Vault:</i>		Angiosarcoma, chondroma, chordoma, lympho-epithelioma.
<i>Hypophyseal Duct:</i>		Epidermoid carcinoma, adamantinoma, dermoids, epignathi, teratoma.

by saprophytes that produce a very foul and malodorous condition in which the patient raises several hundred cubic centimeters of foul sputum per day. The disease is being increasingly dealt with by lobectomy or pneumonectomy, and specimens

habit areas of pneumonic infiltration. The dilated sacs may reach to the pleural surface, but they do not often penetrate it. The microscope reveals the mucopurulent exudate in the lumen of the bronchi, their thinned out walls which may be infiltrated



Roentgenograph demonstrating bronchiectatic sacs in which fluid levels are readily visible. Lipiodol injection. (Col. F. H. Loucar.)

may be examined almost as extensively in the laboratory as in the necropsy room.

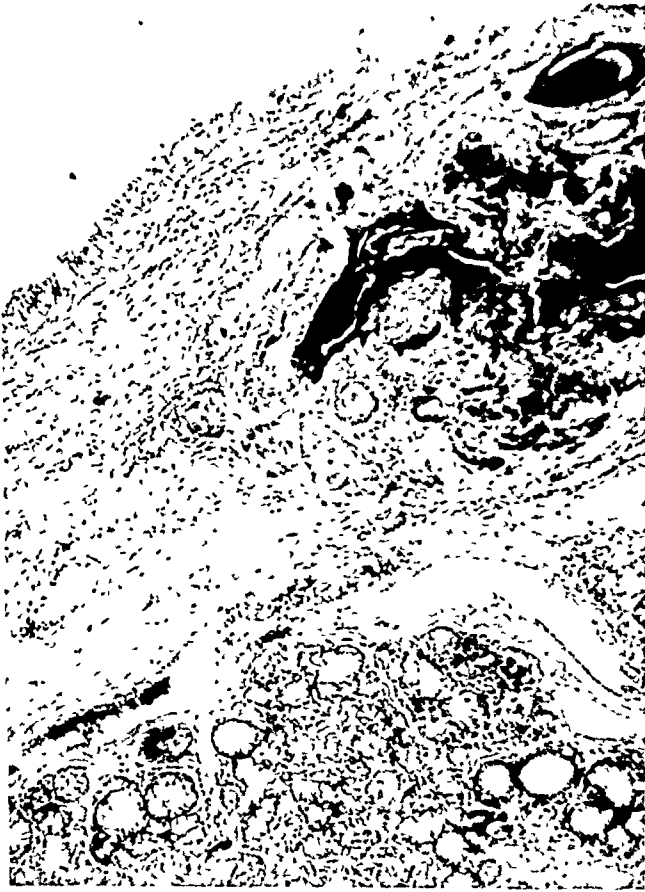
The areas affected are nodular and firm, and upon following down the main bronchi with sharp pointed scissors one traverses several centimeters of comparatively normal bronchus and then enters the long sacs which, when laid open, may measure three centimeters in circumference. They are filled with thick and tenacious yellowish pus and mucus. The pulmonary tissue about them is thickened and fibrotic and may ex-

hibit areas of pneumonic infiltration. The dilated sacs may reach to the pleural surface, but they do not often penetrate it. Usually there are scattered fibrous scars in the neighborhood of the affected bronchi.

Abscess. This usually follows pneumonia in which a focus of infection becomes very intense and destroys the alveolar boundaries with the formation of a soft mass of purulent material and debris surrounded by a firmer zone that is known as the abscess

other cord is also invaded. It is said to be slow about metastasizing; when it does so it goes chiefly to the regional nodes.

SARCOMA. Chondro- and myxosarcoma may originate in the cartilaginous wall of the larynx. Comparatively innocent-looking chondromas may exhibit unsuspected



Laryngeal biopsy showing typical epidermoid carcinoma at upper right and respiratory epithelium to left of this. Below are numerous normal mucous glands.

and unexpected malignant traits and may recur repeatedly, metastasizing locally to the soft parts around the larynx.

TRACHEA AND BRONCHI

The structure of the trachea and the bronchi is essentially similar until one reaches the secondary bronchi and bronchioles, where much of the wall becomes lost and the tubes become largely fibrous and muscular with an epithelial lining. This is at first compound stratified with a superficial layer of ciliated cells; as it proceeds

downward it becomes reduced to a single simple layer near the junction of bronchiole with infundibulum. It is important to remember that there are mucous glands situated between the cartilaginous rings and that the bronchioles are provided with a definite muscular layer. Lymphoid tissue is more abundant than is commonly supposed.

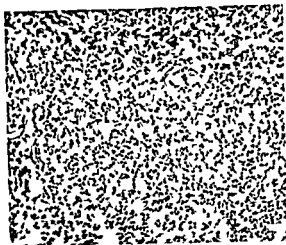
Inflammation. Surgical pathology is not particularly concerned by inflammatory conditions in the trachea and bronchi, as these are medical problems; it is principally their tumors that interest us here. Occasionally a bronchial cast resembling a white tree denuded of foliage will be brought to the laboratory. Investigation proves this to be composed almost exclusively of fibrin with an admixture of inspissated mucus and a few inflammatory cells. These casts are produced in a little-understood condition known as "fibrinous bronchitis," which may be a continuation of a pseudomembranous inflammation of the trachea downward until it involves the bronchi, or a spread upward of a fibrinous pneumonia, or (less often) a caseous tuberculous pneumonia. Sometimes, like membranous colitis, it is ascribed to neurotic etiology—a convenient category that is decidedly unsteady. Nevertheless one can conceive of overstimulation to a mucous membrane resulting in an overproduction of mucus, and we know that mucus is often a product of psychic stimuli (for example, the "ropy saliva" that is secreted during fits of passion or fear).

Bronchiectasis. This is characterized by the dilatation of bronchioles, which may be congenital or acquired as a result of prolonged bronchial inflammation of a sub-acute or chronic type.

CONGENITAL BRONCHIECTASIS. This is often a milder manifestation of pulmonary cystic disease. It takes the form of spherical dilatations of bronchioles, which are not particularly inflamed or foul.

ACQUIRED BRONCHIECTASIS. In this the bronchi are dilated into elongated sausage-shaped tubes with thinned-out walls. They contain mucopus and may become infected

almost bubble thin. They usually occur in patients who show other developmental defects as well. Under the microscope the thicker cysts will reveal remnants of bronchial structure in their parietal tissue, and bits of muscle or cartilage will be found, the thin, blister-like cysts have walls that correspond with those of the air sacs. The condition develops, apparently, as a faulty



Pulmonary "adenoma" of five years' standing. Origin of this tumor is frankly puzzling, it resembles unexpanded fetal lung. Note its excellent differentiation and its lack of metaplasia and of mitoses.

growth of the bronchial buds which ultimately form the pulmonary tissue, so that it represents the dilatation of abortive pulmonary elements which may be accompanied by interstitial emphysema.

Echinococcal Cysts. There is no need to describe these beyond remarking that they may occur in the substance of the lung, or just beneath, within, or on the surface of the pleura. They are considered in connection with the pathology of the liver.

Pulmonary Tumors. Most of the pulmonary tumors have origin in the bronchial tree, so they are, more strictly speaking, bronchial tumors that invade the pulmonary tissue. There are some exceptions, chiefly among the metastatic growths that will be discussed later. We have considered the hyperplasias and metaplasias of the alveolar

epithelium, this might conceivably produce neoplastic growth that originated in pulmonary tissue per se. As we are dealing with organs that include epithelium, collagenous and reticular fibrous tissue, cartilage, vascular tissue, and smooth muscle, together with considerable lymphoid tissue, there is a possibility of a rather broad range of hypothetical tumors, few of which are encountered often enough to be of much importance. Small chondromas and osteomas are occasionally observed.

TRACHEAL ADENOMA. This is usually listed among the nonmalignant tumors of the respiratory tract, but experience is beginning to teach us that it may exhibit malignant forms. It has always been known that it recurs after removal, and this has been attributed to the fact that fulguration through a bronchoscope is not apt to remove such a growth completely. It is usually found occupying recesses in the lining of the trachea or main stem bronchi. It remains flat and unimportant until it begins to grow into a lobulated mass that blocks the air passage, ultimately obstructing it completely. This causes marked disturbance, there may be collapse of the lung distal to the stoppage, or this obstruction may be incomplete if the tumor acts as a ball valve, and air may be pumped into the lung beyond it without being able to escape, causing emphysema. Infection is very apt to complicate this process, filling the bronchial tree with thick pus and mucus and bringing about chronic bronchiectasis.

When the tumor has been removed the dammed up pus is evacuated and may cause infection of other lobes by aspiration. Formerly it was generally believed that this was the chief danger of the tumor, but we have observed two of them in the laboratory—one in consultation and the other over a period of five or more years—and found that they may be malignant. The growth that was observed almost from its inception had ten biopsies taken from it, and the patient was observed during the development of the tumor. She finally succumbed to mul-

"capsule," around which in turn there are areas of pneumonia. The last subsides, but leaves an abscess well installed in the pulmonary tissue. Usually this communicates with a bronchus, but when postural draining fails to empty the abscess cavity it is necessary to "unroof" it surgically and drain it through a communication with the outer surface of the thorax. Fragments of these



Field from inflamed wall of a bronchiectasis. Inflamed epithelium is forming duct-like structures in granulomatous tissue of submucosa.

"unroofings" are frequently sent to the laboratory. They show the gross evidence of long-standing subacute inflammation with fibrosis of the overlying pleura. Microscopic examination reveals a banal abscess with a wall composed of consolidated alveoli, fibrous tissue, and considerable exudate comprising lymphocytes, plasma cells, polymorphonuclear leukocytes, and fibroblasts. In the fibrous tissue one may observe glandular spaces (lined with continuous cuboidal epithelium) which represent pulmonary alveoli that have been isolated from their bronchioles. The epithelium exhibits a return to the fetal type of pulmonary epithelium. Such structures are sometimes mistaken for carcinomatous complexes; this

error should be avoided. Occasionally there will be areas of interstitial pneumonitis of a chronic type in the vicinity of abscesses; this is characterized by chronic exudates in the interalveolar walls and a rather massive exudate of macrophages and desquamated cells into the air sacs.

TRACHEA, BRONCHI, AND LUNGS

From this point on the lungs will be included in the discussion; they have already crept into it, in fact, as we have descended the bronchial tree. They add to the elements already considered the elongated infundibuli at the ends of the bronchioles and the alveolar sacs that open into their rather wide lumina. There is still dispute as to whether the alveolar sacs are lined with epithelium that has, for the most part, lost its nuclei; or whether it is composed of other cells—histiocytes, for example. It is profitless to go into this here. The prompt return of cuboidal epithelium to alveoli that are cut off from the outer air seems to indicate that epithelium is still there, as was formerly supposed. This epithelium may not only be restored, it may also proliferate and become cylindrical and adenomatoid, giving rise to numerous nodules of tumor-like appearance. Bell, in a recent article, describes this hyperplasia in connection with chronic interstitial pneumonitis and sees in it a possible focus for neoplasia; Taft and Nickerson, reporting very recently on two cases, speak of "pulmonary adenomatosis." This has a bearing upon the tumors of the air passages and lung that will shortly be discussed.

The lung itself presents little in the way of surgical pathology; it is its "ducts" or bronchial tree that concern us chiefly. Aside from its cystic conditions, pulmonary cysts, cystic disease, and echinococcus cysts, there is little to be mentioned save the tumors which may beset this organ.

Cystic Disease of Lung. This is a congenital lesion in which one or more lobes of the lungs may show multiple cysts, some of them with thicker walls, some of them

in a collagenous stroma. Masson's theory that carcinoids originate in Kulschitsky argentophil cells of the intestine will not explain the presence of this tumor in the trachea and bronchi. In these situations Stout has found a sort of "reserve cell" which he believes develops into the tumor. As carcinoids are usually found near sympathetic nervous complexes in the wall of the intestine, and as there are similar structures in the walls of the trachea and bronchi, it is probable that these neoplasms arise from nervous elements associated with the ganglia of these. The word "paraganglioma" means just this, and the tumors that go under that name possess argentaffin (also chromaffin) granules. This strengthens the above assumption.

One may say, then, that these growths in the bronchial tree are usually nonmalignant, although malignant forms may be noted and, it must be confessed, are indistinguishable from the malignant variety. The tumor is not very malignant looking, even after it has killed the patient!

CARCINOMA Carcinomas of the pulmonary tree are so nearly exclusively of bronchial or parabronchial origin that they may be said to be bronchiogenic, occasional tumors are observed which suggest alveolar origin, but these usually prove to be bronchiogenic neoplasms which spread out over the alveolar walls from the bronchioles and hence appear to arise from their epithelium. It has been the consensus of opinion that bronchiogenic carcinomas have been on the increase since 1915 or thereabout. As pulmonary carcinoma was hitherto well known as affecting miners in the Schneeberg district of Austria where pitchblende is mined, it was supposed that the increase in incidence of this tumor was attributable to some local irritant. Poison gas during World War I, the increase of road tarring, and Maude Slye's theories on the heredity of cancer were all called in to explain this and ultimately rejected. Recently Steiner has thrown doubt on the theory of increase in the incidence of bronchiogenic carcinoma

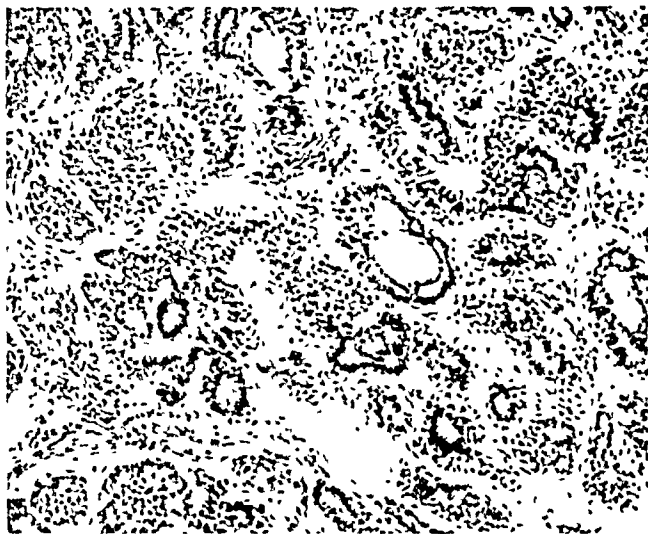
by plotting graphs to illustrate the incidence of carcinoma of the stomach and of the colon against that of this tumor, he finds that all three exhibit strikingly similar fluctuations over the period studied, showing an apparent rise during the past forty years.

The various types of bronchiogenic carcinoma are grossly very similar, they arise as a rule near the bifurcations of the main bronchi near the hilum of the lung, which makes their extirpation difficult. Very occasionally they may originate near the periphery of the lungs. A small tumor of this sort occupying the bronchus near its origin from the trachea can cause a great deal of trouble by obstructing the bronchus and affecting an entire pulmonary lobe. In order to extirpate this sometimes insignificant looking tumor, which may not measure much over $2 \times 1 \times 1$ cm., the entire lobe (or even the entire lung on that side) may have to be ablated. Metastasis to the hilar lymph nodes may occur early and undo all the advantages of such an operation. The tumor is usually white, granular, and hard, but rather crumbling. It may resemble one of the hard varieties of cheese in this respect. It ranges from 1 cm. to 8 or 9 cm. in greatest diameter when exposed at operation.

It is convenient to divide bronchiogenic carcinomas into several groups according to their appearance under the microscope.

Adenocarcinoma This resembles almost any adenocarcinoma and probably takes origin in parabronchial mucous glands and their ducts. It is moderately common.

Epidermoid Carcinoma Like other specialized epithelia, that of the bronchial tree may undergo a surprisingly complete change to the epidermoid or squamous type when inflamed or irritated. This metaplasia may continue to form epidermoid carcinoma. This tumor is solid and may show well defined acanthosis with intercellular bridges and keratosis and with the production of epithelial pearls, or it may be less well differentiated and merely produce masses of poorly formed squamous cells that are only partially keratinized. These grow into solid



Carcinoid of trachea. Note resemblance both to intestinal carcinoids and to "oncocyctic tumors" of parotid region.

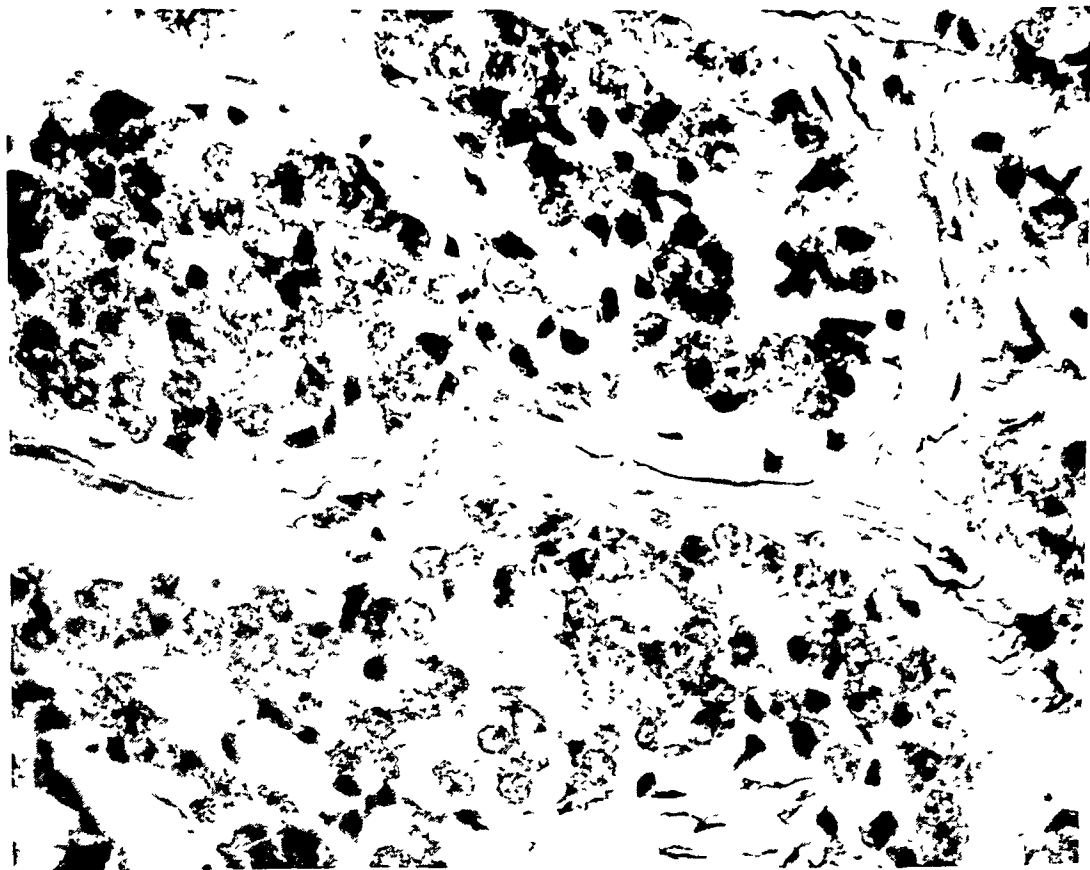
multiple metastases and was autopsied in our hospital, where it was found that there were metastases in the liver, lung, and elsewhere.

Microscopically the tumor resembles two other growths: in one form it is very similar to the carcinoid of the intestinal tract, in

the other to the innocent-looking "oncocyctic" form of salivary-gland carcinoma. Hamperl describes these forms as "bronchial carcinoid" and "bronchial oncocytoma." He believes them to be varieties of the same tumor, and that he is correct is proved by the fact that the neoplasm studied in our hospital showed both forms in most of the biopsies and in the specimens obtained postmortem.

It has usually been found that these tumors, when impregnated with silver, do not give the positive argyrophil reaction that is easily obtained in carcinoids of the intestine; yet in both tumors examined in our laboratory positive reactions were obtained with the use of the standard impregnation for reticulum, which demonstrates not only that tissue, but argentaffin granules.

Of whichever form the tumor may be, the cells lie associated in rounded islands that are either solid or possess a number of acinar lumina; these islands are embedded



Silver impregnation of the tracheal carcinoid shown in preceding illustration in a lower power. This is the first published illustration of argentaffin granules in this tumor; they are readily visible in cytoplasm of cells.

one, the pleomorphic from the middle one, and the "oat celled" type from cells in the basal layer which he calls "reserve cells" This is a pleasant theory and one that lends itself to teaching the subject, but it may be a little too plausible to hold water in all instances

Pulmonary bronchiogenic carcinomas are somewhat peculiar in their routes of metastasis, as they are very apt to involve the spleen, the suprarenals and the kidneys, all of which are organs not usually affected by metastatic tumors In addition to this they take more usual routes to the bones, liver, brain, and other localities

LYMPHOSARCOMA As there is a good deal of lymphoid tissue scattered along the course of the bronchi, as Miller has demonstrated, there is always a possibility that lymphosarcoma may arise in the lungs It needs no description

FIBROSARCOMA Occasionally one encounters fibrosarcoma in the pulmonary tissue, but it is always difficult to decide whether it is primary there or metastatic from an other organ Even in the case of autopsies it is not always easy to make this decision

SECONDARY TUMORS On account of its rich capillary nexus the lung is a favorite site for metastasis from malignant tumors all over the body Those that spread via the circulation send out cells or groups of cells that become entrapped in the pulmonary capillaries and there multiply to set up subsidiary growths Tumors of the breast, prostate, and salivary glands, as well as melanomas of the malignant type, are often found here, fibrosarcomas and osteogenic sarcomas, together with chondrosarcomas and less definitely malignant looking chondromas, also show pulmonary metastasis The reader may amplify this list by thinking up the possible routes of metastasis through the blood and lymph

MEDIASTINUM

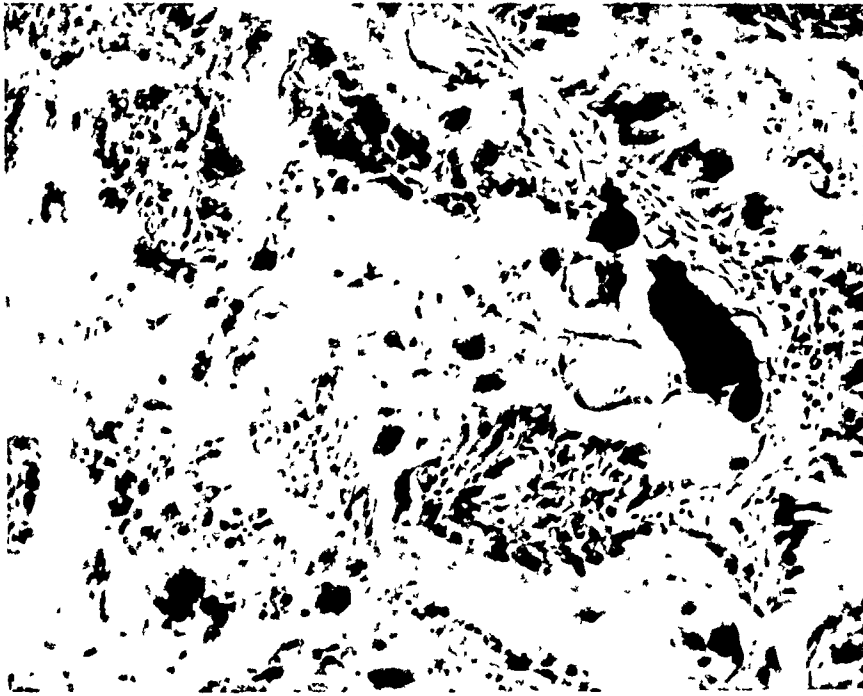
This book would be incomplete without a consideration of the pathology of the mediastinum but it is difficult to fit this

indefinite anatomic cavity into the scheme we have been following It is not an organ nor a tissue, nor is it a system, after all it is merely a rambling series of compartments in the core of the thorax divided into three groups the anterior, middle, and posterior mediastina In the first there is the post sternal space that is largely occupied by the thymus (which is considered elsewhere) and a mass of adipose tissue that serves as "stuffing" and largely replaces that organ in adult life The middle mediastinum contains the great vessels of the heart, the loose tissue about them, the bifurcation of the trachea, and the hilic pulmonary lymph nodes The posterior mediastinum houses the esophagus, thoracic duct, aorta, and other such structures, these are described elsewhere in connection with the systems that they serve Under certain conditions the thyroid and parathyroid glands may descend into the anterior mediastinum or be imprisoned there

Inflammation Mediastinitis is usually a matter of the extension of inflammation from one of the organs just enumerated Puncturing wounds of the esophagus, inflammation of esophageal diverticula, perforation of malignant ulcers, or other such events may also cause inflammatory reactions in the mediastinum This may lead to the production of mediastinal abscesses Acute inflammatory conditions of the thymus may likewise spread to mediastinal tissue Acute or chronic inflammation of the hilic pulmonary lymph nodes may lead to infection and inflammation of the surrounding spaces

Tumors It is the neoplasms of the mediastinum that are of chief importance, as they occupy the indefinite chambers of this cavity and constitute fairly concrete surgical entities that are difficult to allocate to any particular organ (Those of the thymus, thyroid, and parathyroid have been considered elsewhere)

FIBROMA Fibromas may arise anywhere in the mediastinum and grow to considerable size, they do not differ from other



Bronchiogenic adenocarcinoma showing large masses of calcific material, the presence of which is unusual and unexplained. Cells resemble those of parabronchial mucous glands and of bronchial lining by turns.

masses and sheets and invade the infundibula and alveoli.

Pleomorphic Type. Here (as the name indicates) the cells are so poorly differentiated and metaplastic that one cannot recognize their origin; they might come from almost anywhere. Their grouping is not indicative of any particular source. This tumor is more malignant than the better-differentiated epidermoid type, but no more so than the adenomatous.

Undifferentiated Type. In this tumor the cells are small and round, or large and round, or fusiform to blunt fusiform (the "oat-cell"). The so-called "oat-celled carcinomas" are not uncommon among the bronchiogenic group. These undifferentiated tumors are very malignant and metastasize widely.

Alveolar-celled Carcinoma. This is at present purely theoretical. There are some tumors that tempt one to classify them as alveolar in origin. Bell, and Taft and Nickerson, have toyed with the idea in discussing the hyperplasia of the alveolar epithelium in pulmonary disease. One should be on the watch for an opportunity to prove

or to refute the hypothesis; at present it is merely an attractive one.

As an explanation for the various forms just described, Hálpert has postulated a series of layers in the tracheal mucosa from which tumors may originate, the epidermoid type coming from the upper or superficial



Biopsy from intrabronchial tumor showing mass of "oat-celled" carcinoma. Note closely packed, short, plump, fusiform cells composing this variety of bronchiogenic carcinoma.

from nerve roots in the spinal cord or from displaced rests of the ganglionic crest. They may also occur along the intercostal nerves. Neuro epitheliomas, neurilemmomas, neuro fibromas, and ganglioneuromas are the more usual forms noted, although one occasionally encounters the malignant ganglioneuroma here. Many of these are included in the surgical group of "hourglass tumors",



Mediastinal teratoma showing fairly normal cartilage and around this masses of completely undifferentiated cells. These determine malignant nature of tumor.

arising in the spinal canal they emerge through the neural foramina into the posterior mediastinum. Here they grow to larger dimensions, thus attaining an hourglass or dumbbell shape, their slender mid portion being compressed by the bony wall of the foramen.

TERATOMA The mediastinum is a frequent site of teratomatous tumors that appear to arise from misplaced totipotential cell rests. These vary from simple epidermoid cysts, containing sebaceous material and hair, to very complex organoid teratomas that contain bone, cartilage, epithelium of various types, nervous tissue, and other odds and ends of primitive tissue. They may be largely composed of gastrointestinal elements, so that one reads of "intestinal cysts" of the thorax.

The important feature about these teratomas is the fact that within them may lurk large collections of undifferentiated embryonal tissue that show numerous mitotic figures. These areas may ultimately overgrow or destroy the better-differentiated portions of the growth in which they arose. When this occurs they resemble gonadal dysgerminomas and are equally malignant. It is imperative, therefore, to examine several blocks of tissue from different areas of a mediastinal teratoma before passing final judgment; one must rule out the presence of any poorly differentiated elements. If this is possible the prognosis will be good; if dedifferentiated cells are found one can not be certain that the tumor has not already metastasized.



Section of a well-differentiated mediastinal teratoma. Compare this with illustrations of other teratomas, chiefly ovarian (see Chap. 18).

SECONDARY TUMORS There is a tendency in surgical circles to talk of "Pancoast's tumor of the superior sulcus" as though this were something specific. The term is, in reality, merely topographic, for a number of different growths may be found in the superior sulcus and give rise to similar signs and symptoms. They invade the brachial plexus and interfere with the cervical sympathetic nerves, causing "Horner's syndrome." This syndrome appears in the

fibromas. Fibrosarcomas are also seen here occasionally.

DESMOID TUMORS. Resembling fibromas and not to be confused with the tumor of the rectus sheath that goes under the same name and is quite different, these neoplasms are composed of dense, ligamentous fibrous tissue that is very poor in cellular components. They arise in the connective tissue of the mediastinum and may grow to enormous size. One of them, observed in connection with the Thoracic Tumor Registry, weighed over 4 Kg. and completely replaced the lung on its side of the thorax. Desmoid tumors have a quasi-malignant habit of eroding bone and invading other tissue, particularly muscle; they do not metastasize, however, and their microscopic appearance is very tranquil. Their cellular components are few and well differentiated and consist of fibroblasts of an ordinary appearance. Desmoids of the rectus sheath are a form of low-grade myxosarcoma, as a rule; hence they are quite different.

COMBINED CONNECTIVE-TISSUE TUMORS. Myxomas are fairly common in the mediastinum, and, being allied to fatty and to cartilaginous tissue, they are often combined with it in the form of myxolipomas and myxochondromas. The former sometimes grow to be as large as the desmoid tumor just described, filling an entire side of the thorax. They may show malignant transformation.

LIPOMA. As there is a great deal of fat in the anterior mediastinum there is ample opportunity for the development of lipoma or liposarcoma, both of which may attain ample dimensions and be situated anywhere within that space. Lipomas are radiologically characterized by casting a typical shadow: the tumor is fairly dense at its center and fades out around its periphery, where the x-rays are imperfectly blocked. This lends the shadow a halo of lesser density which is almost pathognomonic of lipoma.

XANTHOMA. Xanthomas have been reported. Heuer and Andrus cited two in

their article in Nelson's Looseleaf Surgery, and since this appeared four or five more have been reported. The tumor is well encapsulated, rather waxy, and of a bright orange color. It may be composed of foam cells or of these intermingled with fibroblasts. Sometimes it resembles the giant-cell tumor of tendon sheath in that it contains foreign-body giant cells; in this case one is tempted to infer that the tumor arises in periosteal tissue, possibly of the ribs or sternum. It is in no way malignant.

OSSEOUS TUMORS. Osteomas and osteosarcomas may invade the mediastinum from the thoracic cage. They have been fully considered in the chapter on connective tissue. They may attain large proportions and compress a lung very noticeably.

CARTILAGINOUS TUMORS. These, too, are taken up elsewhere, and what has been said of the bony tumors applies to them as well.

VASCULAR TUMORS. These are very rarely observed, but several have been reported in the literature and are listed at the end of this section.

LYMPHOID TUMORS. The hilic lymph nodes may be the site and origin of any of these tumors or of Hodgkin's disease.

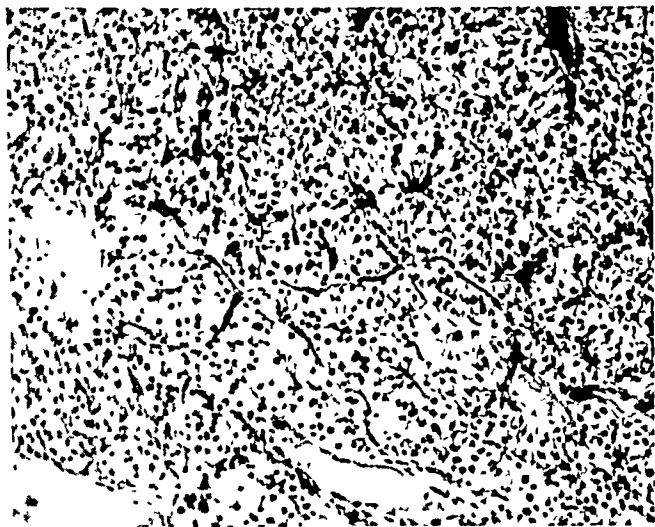
MESOTHELIAL TUMORS. The pleural mesotheliomas may impinge upon the mediastinum and grow into it.

MUSCULAR TUMORS. Polypoid tumors of smooth muscle sometimes arise from the outer walls of the great vessels near their origin in the heart, or from muscular elements of the esophagus. Leiomyosarcomas may occasionally be observed. To be more specific: Kaplan has reported a polypoid leiomyoma at the origin of the left pulmonary vein, Kudlich and Schuh have described a myoplastic sarcoma on the wall of the pulmonary artery, while Catron observed a leiomyoma in the pleura of an old woman. Stout (see Foot reference) found such a tumor protruding from the outer surface of the esophagus.

NEUROGENOUS TUMORS. These are common in the mediastinum, particularly in its posterior compartment, where they arise

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eye on the affected side and consists of apparent enophthalmos, or sunken eye; myosis, or narrowed (contracted) pupil; and pseudoptosis, or a relative drooping of the upper lid, which can, however, be properly elevated. This sign, together with symptoms pointing to a lesion in the apex of the thorax, points to a tumor of the superior sulcus. It happens that most of these tumors are bronchiogenic carcinomas of vari-



Field from superior sulcus or "Pan-coast" tumor. Most of these are bronchiogenic, as this one probably was, but not necessarily so. Other varieties of tumor are found here.

ous types, but one may also encounter neurogenous sarcoma, liposarcoma, and other similar malignant growths.

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13

Alimentary Tract

ORAL CAVITY

CONGENITAL ANOMALIES

INFLAMMATION

TUMORS

MAXILLARY TUMORS

TONSILS

HYPERTROPHY

DEVELOPMENTAL DEFECTS

INFLAMMATION

TUMORS

PHARYNGEAL LYMPHOID TISSUE

'ADENOIDS' AND LINGUAL TONSIL

SALIVARY GLANDS

INFLAMMATION

CYSTS

TUMORS

ESOPHAGUS

CONGENITAL ANOMALIES

DIVERTICULA

TRAUMA

CIRCULATORY DISTURBANCES

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STOMACH

CONGENITAL DEFECTS

STOMACH (*Conti*)

GASTRIC ULCER

INFLAMMATION (GASTRITIS)

TUMORS

DUODENUM

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TUMORS

SMALL INTESTINE

ULCER

CONGENITAL ANOMALIES

VASCULAR DISTURBANCES

INFLAMMATION (ENTERITIS)

TUMORS (SEE TUMORS OF INTESTINAL TRACT)

APPENDIX

ANOMALIES

TRAUMA AND VASCULAR DISTURBANCES

INFLAMMATION (APPENDICITIS)

TUMORS

LARGE INTESTINE

CONGENITAL ANOMALIES

INFLAMMATION (COLITIS)

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TUMORS OF INTESTINAL TRACT

ORAL CAVITY

Congenital Anomalies HARE LIP The commonest congenital deformity of the lips is the condition known as "hare lip," which may or may not be associated with a cleft palate, according to the completeness and severity of the defect. It may be observed in a single or a double form, the former being the commoner. It results from the failure of the median nasal process of the embryo to unite properly with the lateral maxillary processes. Thus the deformity may consist merely of a scar-like raphe that distorts the upper lip, or there may be a notch or a cupping cleft that extends upward into the nostril. Finally, this defect

may communicate with a cleft that runs backward along the median line of the hard palate. There are a number of other possibilities, not so commonly encountered, in which there is more widespread failure of union of the various processes that go to form the palate and the nose. Still rarer is complete agenesis of the lips ("acheilia").

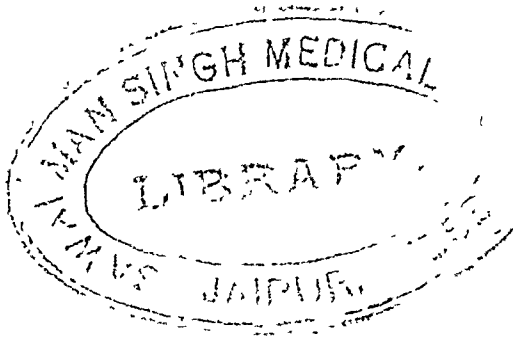
MACROCHEILIA This is a hypertrophic phenomenon in which the lips are larger and thicker than normal; they may attain imposing proportions and give the individual a most unprepossessing appearance. Macrocheilia is usually ascribed to interference with the lymphatics of the lips and the production of lymphedema, or lymphangioma matroid structure, but in a fairly long series

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may be found in the mouth following infection by treponema introduced on contaminated eating utensils or instruments, or in other ways. The secondary stage of the disease is almost regularly marked by the appearance of small white "aphthous" ulcers in the oral cavity. Gumma, the tertiary lesion, may also occur in the mouth. Syphilitic ulcers of the tongue are usually located on the dorsum, they have wavy, irregular borders.

SIMPLE ULCERS may be found in connection with infection of various sorts, such as Vincent's angina or trench mouth, both of which are caused by symbiotic spirochetes and fusiform bacilli. They may also result from vitamin deficiencies, particularly those involving the B complex, in which riboflavin and nicotinic acid deficiency play an important part. Very nasty chronic ulcers may be associated with leukemia.

Tumors NONMALIGNANT By reflecting upon the composition of the oral cavity one may construct a foundation upon which to base a classification of its tumors. As the cavity contains such varied elements as bone, cartilage, muscle, connective and vascular tissue, fat, mucous membrane, and glands, and as the mouth is a complicated embryonal fusion of maxillary and other processes, the chances for a wide variety of tumors are very excellent, the wonder is that the usual run of specimens of tumors from the mouth is so banal.

Tumors of Covering Epithelium The simplest neoplasm of the covering epithelium of the mouth is the epidermoid papilloma, which almost exactly resembles that which occurs on the skin, except that it lacks the extensive keratinization of the latter.

Tumors of Glandular Epithelium The mouth is very richly supplied with small glands that more or less closely resemble salivary glands; they may be found almost anywhere from the lips to the hard palate, in the buccal mucous membrane and the pillars of the fauces. These may form nodules for adenomas and in the case of the palate these adenomas may take the

form of "mixed salivary gland tumors"—a point that is easily forgotten. Many of the myxomas and chondromas of the oral cavity are really tumors of this type. At the base of the tongue there is always the possibility for the development of an aberrant thyroid in the foramen cecum, or a thyroid adenoma. These seem to be ill suited to this environment, for they tend to necrose and to bleed very easily, giving rise to foul masses that call for surgical extirpation. Microscopically they do not differ in their appearance from other thyroid adenomas.

Tumors of Skeletal Muscle A tumor of the tongue that will be discussed under "muscle" has only recently been recognized as arising in that tissue. It forms a yellowish mass in the body of the organ, and when it is examined microscopically it does not resemble striated muscle but looks more like a xanthoma. It is known as "myoblastic myoma" and is discussed fully under the section on myomas.

Tumors of Vascular System Angiomas of the mouth are not uncommon, and they are often potentially dangerous, as they are readily injured and may bleed copiously.

Tumors of Osseous Tissue Osteomas may develop from the palate or maxillae, and there is a tumor like malformation that may occupy the midline of the hard palate and appears to represent a local overgrowth of osseous tissue in the line of fusion of the palatine processes. It is known as a "torus palatinus," and while it is unsightly and interferes with the fitting of upper dentures, it grows very slowly, may become arrested, and is in no way malignant. It forms a nodular elongated excrescence in the midline, extending from the base of the alveolar process anteriorly to the soft palate posteriorly.

Teratomas These are sometimes found in the oral cavity, but they are rare, the very striking epignathic malformations that may sometimes reach the proportion of monstrosities engrafted upon the oral cavity usually interfere so much with oral devel-

of cases at the New York Hospital we have found that the condition usually depends upon a marked hypertrophy of the labial glands—structures that somewhat resemble salivary glands in their histologic composition. With this, it is true, there may be considerable lymph stasis, but the glandular hypertrophy is the more prominent feature.

MACROGLOSSIA. The tongue may show hypertrophic enlargement known as “macro-glossia” in which it becomes enormous and protrudes from an oral cavity too small to contain it. Less commonly it may show a forked extremity (glossoschisis), due to the failure of union of embryonal elements.

HAIRY TONGUE. A familial defect often results in white patches upon the dorsum of the tongue; these are covered with long filiform papillae that lend the patch a hairy appearance; the patch may become coated with a brownish, discolored layer of epithelium.

Inflammation. Of the acute inflammations of the oral cavity few have surgical importance beyond the incision and drainage of abscesses and similar procedures.

NOMA. Extensive gangrene of the angle of the mouth and neighboring cheek may follow such diseases as measles in under-nourished, exhausted children; this is known as “noma.” It is attributed to infection by the spirochete of Vincent and its associated fusiform bacillus; sometimes only the latter may be isolated from the lesions. The microscopic picture of noma does not differ materially from that of any gangrenous condition. (See chapter on Inflammation.)

LEUKOPLAKIA. Chronic reactions are common; some of them are apparently more the consequence of irritation than of true inflammation. Of these the white, thickened patches known as “leukoplakia” are the most usual, and they frequently find their way to the laboratory after excision, either because they are mistaken for cancerous lesions in older subjects or because the surgeon may wish for assurance that they are not malignant in order to safeguard the

patient. They may occur on the oral mucosa, on its buccal surface, or on that of the tongue. Often they follow irritation by poorly fitted dental plates. Microscopically they show a conspicuous overgrowth of stratified squamous epithelium with an outer layer that may appear to be vesicular and “waterlogged” rather than horny and keratinized like that of similar lesions on the skin. One might regard “hairy tongue” as an exaggerated form of this lesion.



Longitudinal section of typical button-like lesion of leukoplakia of tongue. It is representative of leukoplakia in general. There is no hyperkeratosis; instead the thickened superficial layer of cells is pale and “waterlogged.”

LINGUA GEOGRAPHICA. A variant of leukoplakia is the “lingua geographica” of children, in which the patches have a serpiginous outline like those of a map. Microscopically the picture is similar to that of leukoplakia, but it exhibits more submucous lymphoid infiltration and acanthosis of the prickle-celled layer.

INFECTIOUS GRANULOMA. Both tuberculosis and syphilis may cause oral lesions, particularly ulcers that are usually located on the tongue.

Tuberculous ulcers may be the result of inoculation of the tongue by bacteria coughed up from pulmonary lesions. In comparison with the frequency of pulmonary tuberculosis these are very uncommon. They are oval in outline, rather sinuous, and affect the tip of the organ.

Syphilitic Ulcers. Syphilis may occasion a variety of lesions. The primary chancre

x ray Ewing states that the percentage rises to 83 per cent

Hair matrix Carcinoma This term was originated by Mallory because of the similarity of the histology of the tumor to that of hair follicles. This form of neoplasm is always slow growing, and it seldom metastasizes. If it is neglected, however, it will erode the tissue in which it arises and produce destructive ulcers, hence its old name "rodent ulcer." Such a tumor, given sufficient time, can destroy the entire lower jaw until nothing remains but a gaping cavern from which the tongue protrudes, the margins of the opening being composed of raw, secondarily infected granulation tissue. In its early form the tumor is like a small, hard, and very sluggish ulcer with a somewhat fissured and scaly base—a very insignificant looking lesion indeed, but fraught with great potentialities if not completely excised as soon as it is diagnosed. Usually excision with a reasonably wide margin is sufficient to remove all further danger.

Carcinoma of Tongue Here again, tobacco and other irritating factors like the juice of betel nuts are important etiologic agents. Although betel nut chewing is not indulged in in the Western world it is a very common habit in the Far East, particularly in the South Seas. Irritation from the snags of carious teeth or from ill fitting dentures may also be at fault. Chronic glossitis, atrophic glossitis (in the elderly), leukoplakia (particularly in its papillary form), fissures, and lingual ulcers have all been considered as etiologic factors. The metastasis from lingual cancer, unlike that of labial carcinoma, occurs very early in the regional nodes that lie in the drainage area of the tumor, the tip of the tongue is served by the submental, the body by the submaxillary, and the base or root by the deep cervical lymph nodes of both sides of the neck. Most observers according to Ewing, believe that it is inadvisable to promulgate any sort of rules as to metastasis, but that author thought that the more atyp-

ical tumors metastasize more freely, particularly if they are deeply ulcerated. The primary tumor is usually found at the margin or on the under side of the tongue, the dorsum being relatively free from invasion, tumors of the distal portion of the organ tend to be epidermoid in type, while those of the body and root are of either the "transitional" or the lymphoepitheliomatous variety, as there is more lymphoid tissue in that situation. Most of the epidermoid tumors are infiltrating and take a plexiform type of growth.

Microscopically, the epidermoid variety is like epidermoid carcinoma anywhere on a stratified mucous membrane, the "transitional" type is composed of stratified columnar epithelium somewhat resembling that of the urinary tract and hence called "transitional", the lymphoepitheliomatous type will be discussed in connection with the tonsils.

So far as distant metastasis (or let us say "telemetastasis") is concerned, the lingual carcinomas may metastasize to the liver and lung, although this is rare. Ewing cites the statistics of the Middlesex Hospital in London, where, out of 148 autopsies on deaths from lingual cancer, 8 metastasized to the liver, 7 to the lungs, 4 to the pleura, 3 to the suprarenal glands and 2 to the heart. The course of lingual cancer is very rapid, death usually occurring in six to twelve months. In these tumors x ray treatment has improved the prognosis somewhat, the course being to combine block dissection of the regional nodes with irradiation of the primary growth. Martin reports 25 per cent of five year cures at the Memorial Hospital in New York in 550 cases. Radon seeds may be used with or instead of x rays.

Carcinoma of Oral Cavity Carcinomas may develop upon the gums, where dental plates cause irritation, or on the buccal mucosa. These may arise as primary lesions or as direct "kissing metastases" (Abklatschmetastasen) from the tongue to the cheek or gums. The type of these is usually

opment and feeding that the child who bears one dies.

Ranulas. A small cyst under the tongue which is produced by obstruction of a salivary duct of the sublingual gland scarcely rates as a tumor; it is a simple obstruction cyst like any other one due to like causes. It contains some glairy fluid and is lined by the epithelium of the duct.

sue and undergo ulceration by interfering with their own blood supply. In the infiltrative form the basal layer may become very active and form a rete of anastomosing cords of cells—the “plexiform” type of epidermoid carcinoma, which is the most malignant as it is the least well differentiated. Metastasis occurs late and is in direct relationship to the size and degree



Epidermoid carcinoma of lip. Note aggregations of keratinized cells (“pearls”) and invasive appearance of rete cones of epidermis. Furthermore, the epithelium is metaplastic, not uniformly well differentiated.

MALIGNANT OR CANCEROUS. CARCINOMA. Carcinoma of the lip may be of two varieties: the epidermoid, which is derived from the normal stratified epidermis or epidermoid mucosa of the oral region, and the hair-matrix or “basal-celled” carcinoma, which arises from the skin at the mucocutaneous junction.

Epidermoid Carcinoma. This usually occurs in elderly men, preferably clay pipe or cigar smokers and those exposed to the weather. That it can begin in patches of leukoplakia is probable, that it follows syphilitic lesions is less evident.

Like all carcinomas of the surface these may grow out from their base in a papillary form or may invade the underlying tis-

ue of malignancy of the primary lesion. The submaxillary and submental lymph nodes are invaded prior to the deep cervical chains. Ewing states that metastatic lesions developed after hospitalization in 3 out of 224 patients who had lesions 1 to 1.5 cm. in size, while 4 per cent of 276 lesions of a variety of sizes yielded metastases after from one to seven years. The percentage of probable metastasis rises with the size and “grade” of the tumor; Broders found 66 per cent metastases in grades III and IV, with much lower figures in the case of the lower grades. With careful block dissections of the submental and submaxillary lymph nodes the cures may be as high as 78 per cent, with surgery plus irradiation with the

of the embryologic development of the tooth. Macroscopically they are somewhat cyst like affairs embedded in the alveolar processes of the upper or lower jaws, microscopically they fall into several classes, depending upon the degree of differentiation that they may exhibit. (1) they may be composed of epithelium of the prickled variety and may form acanthomas which represent neoplasia of primitive epithelial dental plugs that have persisted in the substance of the jaws, (2) they may show differentiation in the direction of producing dentine and tooth like structures, in which case they are known as "odontomas", (3) the differentiation may take the line of the enamel forming organ and produce the more familiar "adamantinoma" or "ameloblastoma".

1 Acanthoma. These closely resemble epidermoid carcinomas when first viewed through the microscope, although they produce pearls and anastomotic cords of basal cells there is no evidence of invasive growth, and few if any mitoses are to be noted. Prickled cells which show no metaplasia form the bulk of the tumor. The clinical history and the account of the operative removal are of importance in arriving at a diagnosis.

2 Odontoma. In these there are tooth like bits of material which make them angularly nodular and hard. After decalcification and section, one finds a disorderly array of dental building material well formed teeth may be present, or there may be merely embryonal rudiments of these, or again there may be merely a jumbled mass of dentigerous cells of various stages of development. The type cells are odontoblasts, but there may be an admixture of ameloblasts from displaced enamel organs.

3 Adamantinoma (Ameloblastoma). This group is by far the commonest and the most important of these dentigerous tumors or cysts. Ewing considered them all to be of a malignant character on account of their tendency to recur and to invade bony structures in the neighbor-

hood. The tumor is developed from the ameloblast as a type cell. Grossly it is cystic or solid, as the case may be, and occupies a cyst like cavity in the maxilla or mandible, it has a tendency to thin out the bone between itself and the adjacent antrum and to penetrate the cavity of the latter. It usually occurs in adulthood, women being more often affected than men, and it runs a long course.



Adamantinoma (adamantoblastoma) of mandible. There are two types of stroma here: one surrounds gland like cellular complexes and is ordinary connective-tissue stroma, the other lies within lumina of these complexes and is enamel pulp. The latter becomes absorbed and produces acinoid structures like glands.

Microscopically the cystic form is found to be made up of large cavities lined by epithelium which may be smooth or papillary, and the connection of this tumor with the embryonal enamel organ is less evident here than it is in the solid variety. The solid form is divisible, according to Ewing, into three types: an acanthomatous type that resembles that of the odontoma, as it represents a harkback to the primitive epithelium that is common to the production of odontoblasts and ameloblasts, a plexiform type, and a small cystic or glandular type which more closely recapitulates the embryology of the enamel organ. In this form the cysts are, in reality, a strange re-

the epidermoid variety. They are almost as venomous as those of the tongue, killing within two years. Those that arise in the tonsil or pharynx, often of the lympho-epitheliomatous type, have even a shorter course, death ensuing in six to ten months in the case of the tonsillar and in four to ten months in that of the pharyngeal. These, too, are supposed to be susceptible to ir-

EPULIS. Probably the commonest tumor of the gums is the epulis, the name meaning "upon the gum" (*epi oulos*), which is, to say the least, a very broad and inclusive term. These little tumors are usually removed by dental surgeons and seldom reach great size. They are discussed at length in the chapter on bony tumors. Suffice it to remark here that they are not



Extensive infiltration of submucous tissue of tongue by neoplastic lymphocytes in lymphogenous leukemia.

radiation, particularly as they may be attacked very directly without intervening structures to absorb the rays.

OTHER MALIGNANT TUMORS. We have considered hemangiomas of the oral cavity; their malignant variety, hemangiosarcoma, may also be found here. Malignant muscular or bony tumors are a possibility, although they are infrequently encountered. Infiltration of the oral and lingual tissues by leukemic cells is a common phenomenon.

Tumors of Maxillary Tissue. The pathology of the teeth (except for tumors that arise from dentigerous rests in the maxillary processes) belongs elsewhere. The gums are chiefly of interest on account of the tumors they harbor.

found near the permanent molars, but rather in the vicinity of the bicusps and canine teeth, where Geschickter and Copeland believe that they develop from odontoclasts left over from the period of absorption of the roots of the primary or milk teeth. They are giant-celled tumors and differ very little from those that develop elsewhere in bone.

RADICULAR CYSTS. These are small cysts that develop at the roots of teeth and are very simple in their structure, they probably represent the remains of inflammatory processes such as apical plasma-celled abscesses.

DENTIGEROUS CYSTS. These are interesting tumors, rather than cysts, which in their structure run the gamut of recapitulation

that gland. They are also called "adenolymphoma."

Inflammation. Acute inflammatory processes in the tonsil are a "no-le-mo-tangere" in surgery, they should always be treated with great respect, and subsidence of acute inflammation should be awaited before any surgical intervention is attempted.

retention cysts in their crypts. These are filled with malodorous plugs of yellowish desquamated tonsillar epithelium which may be popped out of the crypts by pressure in their neighborhood. The microscopic lesions may show one of two accents: one on the epithelial side and the other on the lymphoid.



This section, which has a resemblance to tonsillar tissue, is taken from a branchiogenic "adenolymphoma." These are usually attributed to parotid origin, but are more probably branchiogenic.

CHRONIC TONSILLITIS. This is a very common malady associated on the one hand with frequent attacks of acute tonsillitis and on the other with rheumatic fever and chorea, together with rheumatic endocarditis. The discovery of what appear to be luxuriant colonies of *Actinomyces* in the crypts of hypertrophied tonsils in children is very common and may be disregarded, as it is an infestation rather than an infection. Actinomycosis of the tonsils is rare, while the discovery of these colonies is very frequent and almost usual in country districts.

Chronic tonsillitis may show two microscopic forms, but grossly it is characterized by tonsils that at first are large and hypertrophic and then gradually shrink in size, becoming scarred and distorted and showing

Chronic "Follicular" Tonsillitis. The crypts are distended and filled with debris and masses of bacteria; there is a pericryptic infiltration of the tissue by leukocytes, often polymorphonuclear neutrophils, lymphocytes, plasma cells, and like elements of subacute inflammation form these. The epithelium of the crypts tends to proliferate and to invade the surrounding lymphoid tissue in the form of interlacing bands. The lymphoid apparatus is not very abnormal. With time, connective tissue overgrowth produces scar-like trabeculae in the organs. Abscesses may be found in occluded crypts.

Chronic Lymphoid Tonsillitis. In this form the picture is indistinguishable from that of chronic lymphadenitis; there is generalized hyperplasia and a great deal of

versal of one's conception of a cyst: the cells form a saccular structure with their nuclei next to the "lumen" instead of away from it, while the "lumen" may contain a delicate stroma of connective tissue and vessels that represent the enamel pulp. This, in normal embryology, deposits its enamel on the surface of the tooth and then disintegrates; in the tumor the disintegration occurs and leaves a true cyst behind. Thus the picture becomes more and more confused. Some of these growths may actually produce a little enamel, but most of them may be sectioned without decalcification.

It is puzzling that adamantinomas may be found as far afield as in the tibia or fibula; they are more readily explained when found in craniopharyngiomas.

GIANT-CELLED TUMOR OF JAW. This is described under bony tumors. It is a form of giant-celled tumor of bone that is very frequently noted in the mandible, involving as much as half of that bone and necessitating disfiguring resection. Naturally, the jaw is not immune from other bony tumors.

TONSILS

These organs are composed of lymphoid tissue with a covering layer of epidermoid epithelium which is thrown into numerous folds that continue into the depths of the organ in the form of crypts. The lymphoid tissue is arranged in follicles like those of a large lymph node. The "capsule," which is removed with the organ in tonsillectomies, contains many mucous glands and some of the skeletal muscle of the faucial pillars. The tonsils are prey to the same general type of pathologic conditions as those from which the lymph nodes suffer, so that we need discuss only those that are more or less peculiar to the tonsil; the rest are taken up in Chapter 11.

Hyperplasia. Probably the most common finding in specimens of tonsils that form the surgical pathologist's daily routine is hyperplasia unaccompanied by any striking pathologic lesion. Such tonsils are removed by the hundreds in the average gen-

eral hospital as a prophylactic measure. Aside from the chance discovery of patches of subacute or chronic inflammation about the crypts, they afford most uninteresting pathologic specimens.

Developmental Defects. As the tonsil is derived from the second pharyngeal pouch, closely associated with the first and second branchial clefts, it is not uncommon to



Lining of a very simple monolocular branchiogenic cyst. Epidermoid epithelium and underlying lymphoid tissue have some of the appearance of tonsillar tissue. (Compare with adenolymphoma shown on page 205. They appear to be closely related.)

find an estray of tonsillar tissue in the neck, quite separate from the tonsil. Such structures are mistaken for tuberculous lymph nodes, and after excision they may present multilocular cysts filled with a brownish, puriform material that is thin and slightly glairy. Microscopic sections show lymphoid tissue surrounding crypt-like structures lined with either an epidermoid epithelium like that which covers the tonsil and lines its crypts, or a simpler columnar type which may look somewhat metaplastic and primitive. These rests may be fairly solid, so that "branchial rests" would be a better term than the usual appellation, "branchial cysts." There may also be some cartilage in these tumors which might lead to their being mistaken for mixed tumors of parotid origin, since as a rule they lie near

arises from the epithelium and forms a papilloma that is firm and white, that may be either smooth and knob like or papillary and feathery, and that projects from the surface into the pharynx. Microscopically these tumors are exactly like those of the skin, except that they exhibit little or no keratinization of the surface layer of epithelium. They are composed of a fibrous

mor, killing in six to ten months and metastasizing early to the deep cervical nodes. It forms large ulcerating tumors that cause extensive necrosis and consequent fetor of the breath. Microscopically it shows hyperkeratinization and the formation of keratinized pearls. It may present three subtypes of growth: keratinizing and slowly progressive acanthomatous (composed chiefly of



Section from epidermoid carcinoma of tonsil, to show how it differs from transitional variety. It simulates epidermis in its cellular arrangement and architecture.

core covered with thick epidermoid epithelium or with feathery papillae of epithelial cells. The lymphoid tissue produces no nonmalignant tumors that may with certainty be recognized. Theoretically nonmalignant lymphomas are a possibility, but they are so closely imitated by focal hyperplasia in the presence of chronic inflammation that it is not safe to attempt to diagnose them. Fibromas may occasionally be found.

CARCINOMA. There are three types of carcinoma of the tonsil: epidermoid, transitional celled, and lympho-epithelioma.

Epidermoid Carcinoma. This resembles epidermoid carcinoma of any stratified epithelial surface. It is a very malignant tu-

mor, killing in six to ten months and metastasizing early to the deep cervical nodes. It forms large ulcerating tumors that cause extensive necrosis and consequent fetor of the breath. Microscopically it shows hyperkeratinization and the formation of keratinized pearls. It may present three subtypes of growth: keratinizing and slowly progressive acanthomatous (composed chiefly of

prickle cells), and plexiform, invasive, and rapidly growing.

Transitional celled Carcinoma. Ewing has accepted this nomenclature, although the histologists reserve the term "transitional" for epithelium of the urinary tract. The circumlocution "stratified columnar" is rather cumbersome when applied to a tumor, so that one might as well bow to usage and accept "transitional celled" carcinoma as the term of choice. These tumors make up the bulk of the malignant epithelial tumors of the fauces. They are composed of sheets and cords of columnar cells that grow in a plexiform fashion; these are much like those of the plexiform epidermoid carcinoma, but they tend to be columnar

migration on the part of lymphocytes, which form long blue streaks in the neighborhood of the "capsule" where they tend to congregate in consolidated masses. There is, however, a good deal of degeneration in the epithelium of the crypts, with infiltration



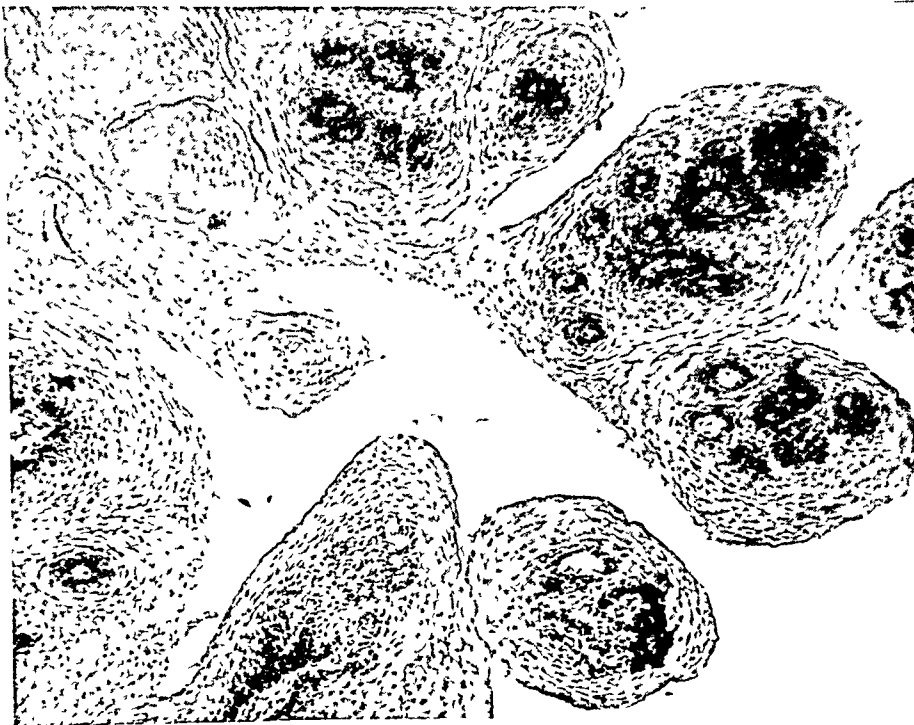
Tuberculous lesion in section of tonsil. Note that it is frankly tuberculous and does not resemble the pseudotubercles in dirty crypts, which are often mistaken for specific tubercles. They are common, while this is relatively uncommon today.

of the surrounding lymphoid tissue by reticular cords of epithelial cells.

These two forms of chronic tonsillitis are probably merely types, rather than strictly different classes of inflammation; they so often merge one into the other that it would be ludicrous to insist upon regarding them as separate entities. Frequently there is a foreign-body reaction to the epithelial debris in the crypts; this should not be mistaken for tuberculosis. Many instances of "tuberculous tonsillitis" really represent these focal foreign-body reactions and are not specific tuberculous infections at all.

SPECIFIC INFLAMMATION. The tonsils may be the seat of specific infections such as tuberculosis, syphilis, and the like; in this case the lesions are typical and need no further description.

Tumors. Being composed of lymphoid and epithelial tissue, with an admixture of reticular and fibrous stroma, the tonsils may harbor tumors of these tissues. Probably the commonest is the epidermoid papilloma, a small noncancerous tumor that



Simple epidermoid papilloma of tonsil. These are relatively common and quite innocent, but they are removed in order to preclude any chance of their becoming malignant.

arises from the epithelium and forms a papilloma that is firm and white, that may be either smooth and knob like or papillary and feathery, and that projects from the surface into the pharynx. Microscopically these tumors are exactly like those of the skin, except that they exhibit little or no keratinization of the surface layer of epithelium. They are composed of a fibrous

mor, killing in six to ten months and metastasizing early to the deep cervical nodes. It forms large ulcerating tumors that cause extensive necrosis and consequent fetor of the breath. Microscopically it shows hyperkeratinization and the formation of keratinized pearls. It may present three subtypes of growth: keratinizing and slowly progressive acanthomatous (composed chiefly of



Section from epidermoid carcinoma of tonsil, to show how it differs from transitional variety. It simulates epidermis in its cellular arrangement and architecture.

core covered with thick epidermoid epithelium or with feathery papillae of epithelial cells. The lymphoid tissue produces no nonmalignant tumors that may with certainty be recognized, theoretically nonmalignant lymphomas are a possibility, but they are so closely imitated by focal hyperplasia in the presence of chronic inflammation that it is not safe to attempt to diagnose them. Fibromas may occasionally be found.

CARCINOMA. There are three types of carcinoma of the tonsil: epidermoid, transitional celled, and lymphoepithelioma.

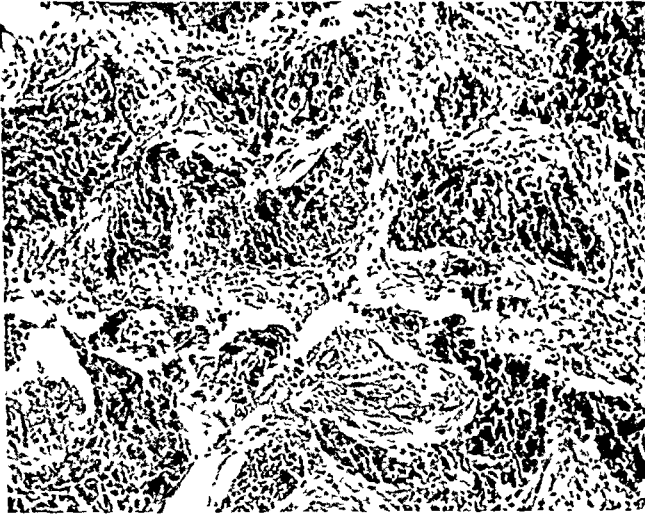
Epidermoid Carcinoma. This resembles epidermoid carcinoma of any stratified epithelial surface. It is a very malignant tu-

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prickle cells), and plexiform, invasive, and rapidly growing.

Transitional celled Carcinoma. Ewing has accepted this nomenclature, although the histologists reserve the term "transitional" for epithelium of the urinary tract. The circumlocution "stratified columnar" is rather cumbersome when applied to a tumor, so that one might as well bow to usage and accept "transitional celled" carcinoma as the term of choice. These tumors make up the bulk of the malignant epithelial tumors of the fauces. They are composed of sheets and cords of columnar cells that grow in a plexiform fashion; these are much like those of the plexiform epidermoid carcinoma, but they tend to be columnar

and stratified, rather than fusiform or polygonal. The tumor invades the base of the tongue and the pharynx as well as the tonsils. It may grow very rapidly, its cells becoming very dedifferentiated and disassociated, in which case diagnosis is sometimes difficult. It invades the local lymph nodes very early and may metastasize widely throughout the liver and lungs, killing the patient in from four to ten months. The



Part of "transitional-celled" carcinoma of tonsil. Solid masses of compound columnar epithelium are distributed through a rather compact fibrous (instead of lymphoid) stroma.

tumor is supposed to yield rather well to irradiation, which should be combined with resection of the local lymph nodes.

Lympho-epithelioma. This cancer is closely related to the transitional-celled type, as it is composed of cords of these cells, which form septa enclosing masses of lymphoid tissue that takes on malignant characteristics and resembles lymphosarcoma, so that one has a tumor in which both epithelium and lymphoid tissue show malignant changes at the same time. This neoplasm was first given the name of lympho-epithelioma by Régaud, and later Schminke described a series of similar tumors, among which he included growths in various other situations, including the thymus. It may be that he went too far in his grouping, which is rather generalized. This tumor is very prevalent in China, where it occurs

almost as often in the nasopharynx, and even within the nose, as it does in the tonsils. It, too, is considered to be a favorable risk for irradiation, but the tumor's rapid subsidence is in line with that of lymphosarcoma under similar treatment, and it may recur after apparently favorable results.

LYMPHOSARCOMA. The various forms of lymphosarcoma described under the lymphoid tissue may attack the tonsil as well; this also holds good for Hodgkin's disease and the leukemias. Such tumors are discussed in the appropriate chapter and need no further mention here.

ANGIOMA. Hemangioma and lymphangioma may be found in the tonsil, where they grow out into the fauces and obstruct the passage, at the same time presenting a hazard to trauma from sharp objects like bits of bone or injury from so humble an instrument as a toothbrush. The writer has seen one patient who suffered from hemangiosarcoma of the tonsil and was nearly exsanguinated from loss of blood occasioned in this manner. The tumors are extremely difficult to deal with on this account, any operative procedure being attended by dangerous hemorrhage. Ligation of the carotid arteries may give temporary relief, but collateral circulation soon offsets this. The most efficient way of treating these growths is probably irradiation, in the hope of thrombosing their channels and destroying the endothelium of their vascular walls.

LYMPHOID TISSUE OF PHARYNX

The lingual tonsil and the so-called "adenoids" may show pathologic changes that are in keeping with those already described in the case of the tonsils.

Adenoids. Most tonsillectomies performed on children are accompanied by "adenoidectomies." "Adenoids" are small collections of lymphoid tissue covered by stratified epithelium and resembling rather rudimentary tonsils. They measure about 1 cm. in diameter and protrude from the pharyngeal wall into its cavity, where they

can be scraped off with the overlying epithelium with relative ease. Under the microscope they look like poorly designed and executed tonsils and show hyperplasia of the lymphoid tissue that composes their bulk. They are of relative unimportance except for the obstruction they present to breathing and the consequent facial deformity which results from their presence.

The lingual tonsil is not very different from the adenoids. One may conceive of a ring of lymphoid tissue surrounding the pharynx, the faucial tonsils occupying the longer sides, the adenoid tissue the upper segment, and the lingual tonsil the lower

SALIVARY GLANDS

The parotid, submaxillary, and sublingual salivary glands constitute the chief members of this group, but (as has been said before) there are many similar glands scattered about the oral cavity. The greatest number of these are in the faucial pillars, the hard palate, the buccal mucosa, and the lips. They show one or two types of glands (serous or mucous) according to which salivary gland one observes: the parotid is purely serous, while the submaxillary and the submental are mixed serous and mucous. These histologic differences are not reflected in the pathology of the glands to any appreciable extent.

Inflammation. Acute inflammation, which occurs oftenest in the parotid gland, is not usually treated by surgical intervention. It may be a pyogenic infection in run-down individuals, or it may take on the familiar endemic form of inflammation known as "mumps," which in adults is not limited to the salivary glands, but may also involve the testis or ovary and the breast. The chronic forms that lead to or result from the formation of calculi in the ducts are often explored in order to remove these and free the ducts from obstruction. The glands become fibrotic and firm, and in the microscopic picture the fibrosis is conspicuous together with diffuse lymphocytic infiltration.

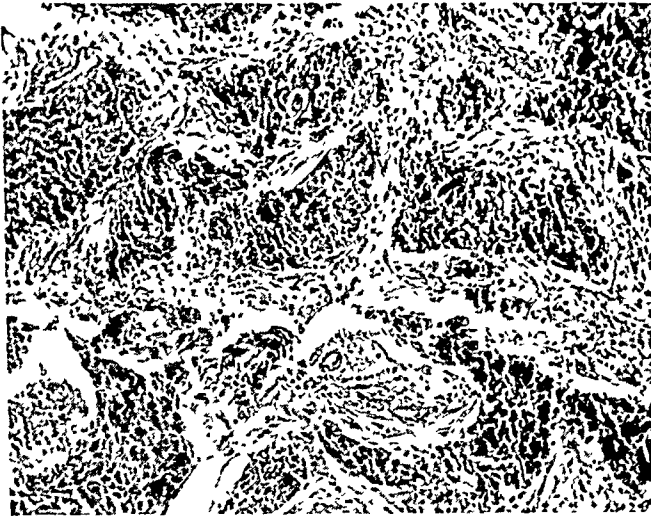
Cysts. These may form in salivary ducts as a result of atresia or obstruction of the passage, or from the presence of congenital defects which Aschoff believed to be similar to those of the congenital polycystic kidney. Those which follow blocking of the ducts by stones are usually located in Wharton's ducts. Such cysts, whatever may be their etiology, may constitute the "ranulae" already referred to.

Tumors. **ADENOMA.** This is very rare, most of the instances described in the literature having turned out to be something else when carefully analyzed. It has a tendency to be cystic, with the cysts varying in size and being separated by fibrous septa. There may be a considerable production of mucus, which then accumulates in the cysts. The epithelium of the tumor tends to reproduce that of the salivary glands in its appearance. Such tumors are well encapsulated, grow very slowly, and contain no "mixed" elements.

CARCINOMA. Ewing recognized three types of carcinoma of the salivary gland: an adenocarcinoma, an alveolar form, and possibly a diffuse form composed of cylindrical and spherical cells. These all form hard, poorly defined tumor masses that are difficult to diagnose either macro- or microscopically; their lack of delimitation is the best criterion one has.

Adenocarcinoma. The adenocarcinoma may reproduce the appearance of salivary epithelium rather well, so that one might deduce its origin from this; it may be simple or papillary in its morphology. A certain type of adenocarcinoma has been called "cylindroma," as it resembles the cylindromas of the scalp, known as "Brooke's disease" by the dermatologists. It has also been called "oncocyoma" by Humberl, who believes that it represents a neoplasm derived from hypothetical "reserve cells" or polyblasts that reside in the salivary tissue. Both these terms leave much to be desired. "cylindroma" is derived from the German word for a urinary cast or "cylinder" because of cast like structures among the cell

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salivary glands is given by Kuttner as 90 per cent in the parotid, 10 per cent in the submaxillary, and 1 per cent in the sublingual (These figures are as Ewing cited them, apparently the sum of the percentages was overlooked) Ewing believed this to be too high an estimate for the parotid incidence Warthin collected 13 instances in the lacrimal gland, other situations noted

histologic appearance of the adenocarcinoma Usually, however, the cells are strewn in the form of cords or duct like structures in the mucoid stroma, thus lending the tumor a decidedly malignant appearance Mitotic figures, however, are seldom present

The mixed tumors are surrounded by an aura of mystery and dispute, one school



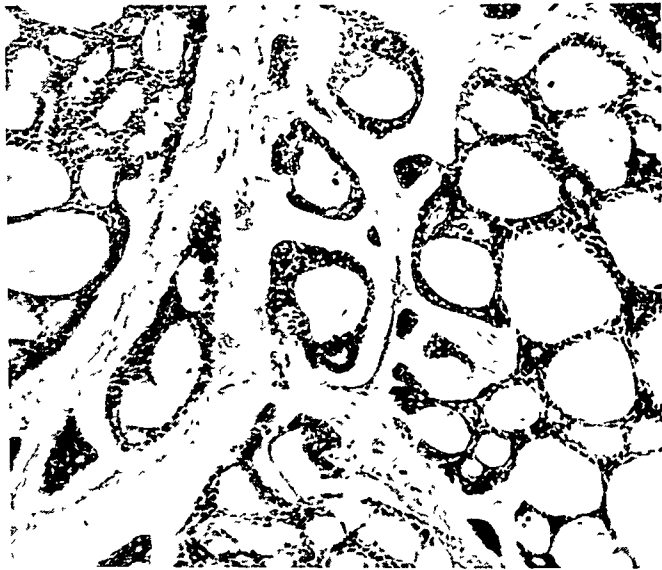
Mixed tumor of parotid Pale areas represent cartilaginous portion of growth A few glandular structures are present, but most of the tumor is solid

have been the antrum of Highmore, the nares, and the tonsils, besides those already mentioned as occasional sites (lips, buccal mucosa, etc) As salivary tissue is present in most of these situations it is incorrect to speak of "aberrant salivary tissue" in this connection

Microscopically the tumors are composed of complexes of epithelial cells, connective tissue that is mucoid in type, and a substance that is variously spoken of as "cartilage" or "pseudocartilage", some authorities believe it to be the one, some the other This may undergo calcification and ossification The epithelium may present adenoid grouping of its cells, reminding one of that of the "epithelioma adenoides cysticum" or "cylindroma" and closely resembling the

maintains that they represent mixed teratoid growths from the buccal epiblast (in which case the matrix is true cartilage), while another (to which Ewing adhered) defends with equal stoutness the hypothesis that they are derived from salivary epithelium which, by reason of its ability to secrete ptyalin and mucus, has the power to transform the connective tissue collagenous stroma into mucoid tissue and thus to pseudocartilage or possibly true cartilage Experimental ligation of the salivary ducts in dogs is said to produce mixed tumors, operations that remove part of the gland and thus interfere with its secretion may give similar results Apparently the tumors may arise in salivary tissue irrespective of whether or not it lies in the immediate

complexes, while "oncocyoma" is a tumor of "oncocytes" which (translated) are "tumor cells." "Tumor-celled tumor" is the



"Oncocytic" type of slowly progressive carcinoma of parotid gland. Note misleadingly innocent appearance of this tumor, which killed the patient by metastasizing to the lungs after fifteen years of recurrences and slow invasion.

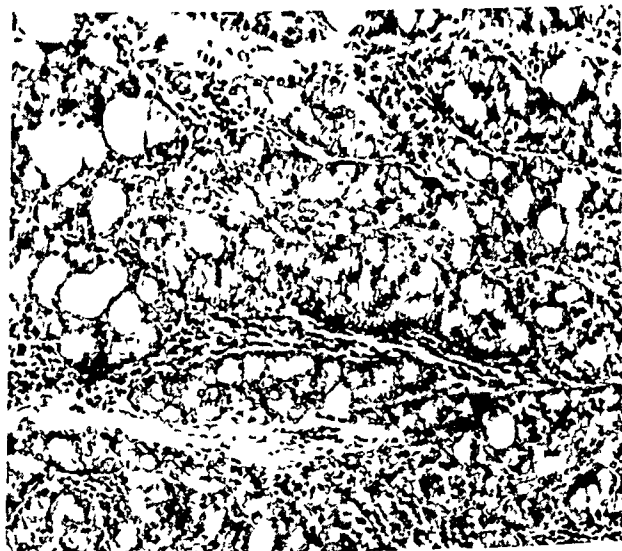


Disarmingly innocent-looking metastasis from carcinoma of parotid. This occurred at angle of mouth some time after primary tumor of parotid of that side had been ablated. Tumors of salivary glands are particularly tricky when it comes to prognosis.

result achieved. Call it what we may, the tumor is a treacherous one because it is poorly demarcated and infiltrating, may grow slowly and recur after repeated removals, and yet look very innocent and well differentiated in microscopic sections. Here it is seen to be made up of well-differentiated

polygonal cells arranged in a multi-acinar pattern. Its nature belies its microscopic appearance, as it metastasizes to the lungs, where it develops very slowly but has an ultimately fatal outcome.

Papillary adenocarcinomas may originate in salivary ducts; the poorly differentiated and diffuse form is readily recognized as malignant, but its cellular components are not indicative of its genealogy. They may



Section of carcinoma originating in parotid gland proper. It is materially different from those arising in mixed tumors of parotid region.

resemble those of a sarcoma, they may undergo keratinoid degeneration, and they may contain or even secrete mucus. They remind one of the epithelial elements of some forms of the mixed tumor of salivary glands, described below.

MIXED TUMORS OF SALIVARY GLANDS. As already indicated, these may be found not only in the chief salivary glands, but also in those of the hard palate, buccal mucosa, or lip, and paradoxically they may be found in the long bones of the extremities, as are the adamantinomas. They are usually slow-growing, and they form swellings that gradually increase in size until they may be ten or more centimeters in diameter. They are generally ovoid, but they may be lobulated. The majority of them are found in patients between the ages of 20 and 40. The proportion of their incidence in the three main

trachea shortly above its bifurcation. There are a number of variants of the deformity, such as both ends of the esophageal segments opening into the trachea, or both being closed. The failure of development occurs very early, it has been reconstructed by Lewis in a 50 mm embryo in the form first described above.

Surgeons formerly attempted to keep children with this anomaly alive by performing a gastrostomy in the hope that they would live until they were large enough to be more successful risks for the major operation of reconstructing the esophagus. This attempt was always frustrated by the regurgitation of milk into the trachea through the gastric segment of the faulty esophagus. At present it has been found possible to tie off this segment below its entrance into the trachea, carry out the original idea of performing a gastrostomy, and thus keep the child alive until the more complicated procedure may be undertaken.

Diverticula There are two types of these traction and pulsion. The former results from traction by adhesions with neighboring lymph nodes which have undergone inflammation and produced adhesive scars, the latter is more truly a diverticulum and usually occurs at the site of a congenitally weak spot in the wall. Either type may ultimately attain considerable size and retain sufficient food to bring about inflammation of its walls through decomposition of the ingested material. The esophagus is normally constricted near the level of the larynx, at the bifurcation of the trachea, and as it passes through the diaphragm, diverticula are prone to occur in these situations.

Trauma Wounds of the neck may penetrate the esophagus, but the more commonly noted esophageal lesions usually result from trauma caused by the lodgment in the esophagus of foreign bodies such as bits of bone, dental plates, or parts of such plates. Further injury may result if these accidents are followed by too zealous and insufficiently skilled use of the esophago-

scope. The lesions, trifling in extent, lead to widespread infection of the periesophageal tissue and that of the anterior mediastinum. Naturally the foreign bodies are apt to lodge at one of the points of constriction. The resulting abscesses are very often fatal.

Circulatory Disturbances Esophageal varices result from obstruction to the portal circulation, particularly in connection with portal cirrhoses of the liver and Banti's syndrome. The blood, unable to enter the porta, backs up into the coronary and gastroepiploic veins of the stomach and thence to the plexus of veins in the esophagus. The resulting varices often give rise to copious hemorrhage.

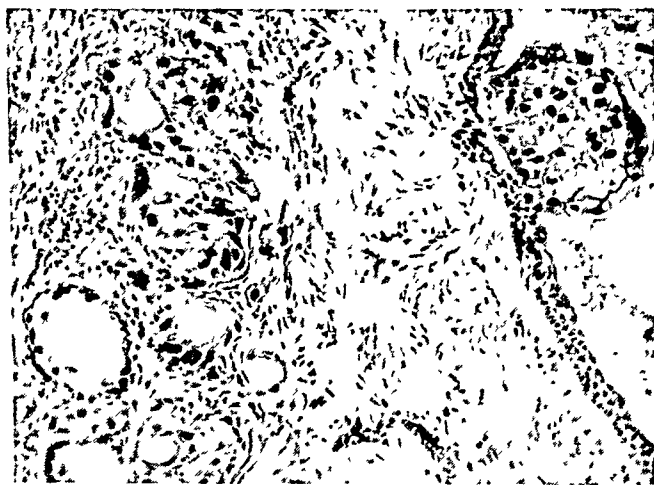
Inflammation Chronic irritation by strong spirits or the ingestion of escharotic liquids like lye and phenol may give rise to weaker or stronger inflammatory reactions. The first type (alcohol) may result in leukoplakia, exactly similar to that seen in other such mucous membranes, the second type involves extensive destruction of the organ and, should the patient survive the ordeal, ultimate cicatrization. The children of washerwomen who use solutions of lye seem very prone to imbibe their mother's cleaning fluid, for most cases of strictures following the ingestion of lye appear to occur in these families.

Specific chronic inflammation does not play a very important role in the pathology of the esophagus. Three types of esophagitis—nodular, follicular, and cystic—are described, but they do not call for surgical intervention and are mentioned only in case the pathologist should encounter them in biopsies of esophageal tissue in which the presence of cancer has been suspected and is to be confirmed or denied. Ulcers may occur in connection with peptic gastric ulcer, tuberculosis, and (very rarely) typhoid fever.

Tumors **ADENOMA** As there are mucous glands in the wall, although the epithelial lining is not glandular, it is possible to find adenomas developing here. These may take the form of small polyps so like those of the

vicinity of branchial clefts or other embryologic raphes. A recent paper on the subject claims that the tumors originate from changes in the myo-epithelial layer of cells in the salivary glands. The reader must be left to make his choice of the theories presented; the subject is still too confused to permit of a categoric statement.

In diagnosing these growths care must be exercised not to overlook true carcinoma. Ewing mistrusted the mixed tumors to such



Carcinoma developing in mixed tumor of parotid.

an extent that he classified them all as carcinomas, making three groups: myxochondrocarcinoma, basal-celled carcinoma with hyalin stroma, and adenoid cystic epithelioma. This classification is misleading, as the tumors (when they are well encapsulated) are not necessarily malignant and as it implies that one of the types has dermal origin (adenoid cystic epithelioma). On the whole, it would seem better not to attempt too strict a morphologic classification, as the tumors are truly mixed in their composition and the resulting pictures are correspondingly variable. One should remember the components: epithelium that is more or less glandular, connective tissue that may be mucoid and usually is, and a substance that is readily mistaken for cartilage if it is not that tissue.

Wide excision of the mixed tumors is the treatment of choice. They do not respond well to irradiation therapy, and if they are

found to be well encapsulated they may be removed in toto. If they are of the poorly defined and infiltrating type, however, the prognosis is bound to be grave in spite of anything that may be done. Fortunately, most of those observed in the course of everyday routine are well encapsulated and small and do not tend to recur.

ENTODERMAL CYSTS. Both Ewing and Boyd classify these as derivatives of the salivary glands; they are described elsewhere in this book under the terms "branchiogenic rests" and "branchiogenic tumors." Their resemblance to the tonsil is far closer than it is to the salivary glands, and their bulky masses of lymphoid tissue is quite unlike anything in the mixed tumor. They are sometimes known as "adenolymphoma."

ESOPHAGUS

The esophagus is a tube lined with epidermoid epithelium, surrounded by smooth muscular coats, and furnished with a few para-esophageal glands which secrete mucus through small ducts that penetrate the epithelium to empty into its lumen. It develops coincidentally with the trachea from a column of cells in which lumina become hollowed out until esophagus and trachea are separated by a transverse partition.

Congenital Anomalies. As a result of its form of development it is quite possible for the esophagus to have faulty areas in which the separation is incomplete, and such defects will cause atresia of the esophagus whereby it is interrupted over considerable portions of its course between the mouth and stomach. In the most usual variety of malformation the esophagus continues from the pharynx for two or three centimeters and ends in a rounded and completely closed process from which a cord (marking the vestiges of the esophageal primordium) continues downward to be lost on the posterior surface of the trachea. At the same time the lower portion of the esophagus runs upward a short distance and then switches anteriorly to open into the

question The prognosis in carcinoma of the esophagus is always questionable, as the operative risks are great and it often happens that the tumor is much more extensive than was believed before the operation was begun Carcinomas at the lower end of the esophagus, involving the cardiac end of the stomach, are difficult to extirpate on account of the fact that they involve both thorax and abdomen, the approach is difficult, and the possibility of restoring the continuity of the esophagus is frequently prevented by mechanical problems

STOMACH

Congenital Defects The only defect of great importance to the surgeon is that in which there is hypertrophy of the pyloric sphincter A description of this is scarcely necessary beyond noting that the sphincteric muscle forms a firm, hypertrophic, doughnut like ring that effectually interferes with the emptying of the contents of the organ into the duodenum Sometimes, when performing the plastic Rammstedt operation for correcting this obstruction, the surgeon excises a small piece of the sphincter as a biopsy, this will show decided hypertrophy of its fibers but nothing else

Gastric Ulcer There is a stupendous literature on this subject, and we shall consider it only from the fundamental, descriptive standpoint, leaving the reader to browse elsewhere for theories (of which there are plenty) and clinical data

HEMORRHAGIC EROSION The simplest ulcers are "hemorrhagic erosions," which are of little importance in surgery unless some should be present in a specimen removed at operation for some other condition They are very superficial little defects in the mucosa, usually seen in the fundus and constituting pinhead sized lesions that either show fresh bleeding points or are almost black and covered with pigmented cloughs They are noted more often in children than in adults, but may occasionally be encountered in adult stomachs Aschoff devoted two closely printed pages to this

subject, mentioning vascular, chemical, and mechanical causes as possibilities, but finally throwing the whole matter open to the reader's choice

ACUTE ULCER (PEPTIC ULCER) These are often multiple and tend to be arranged in rows along one or another curvature, preferring the posterior gastric wall They vary in diameter from a couple of millimeters to a centimeter or so, are shallow, and present inflamed punched out margins that do not



Topographic view of an entire pyloric ulcer Note punched out crater and lack of overhanging, overgrowing epithelial tissue at rim

project above the level of the surrounding mucosa Under the microscope they show a zone of necrotic slough over the surface of the "bed," beneath which there is a band of leukocytic infiltration that fades into the surrounding muscle One may find protruding ends of vessels of a millimeter or more in diameter projecting into the ulcer bed like nozzles, the extremity being either patent and covered with fresh hemorrhage or thrombosed and occluded It is often surprising how small such "bleeders" may seem in proportion to the massive hemorrhage they have occasioned

Theories as to the etiology of peptic ulcers are numerous and fall into three groups (1) agents which act upon the mucosa and destroy it, (2) vascular lesions which interfere with the circulation of the mucosa through thrombosis, arteriosclerosis, etc., and (3) "constitutional causes," such as the "ulcer habitus" and other de

rectosigmoid that they have been mistaken for these on microscopic examination and a "repeat biopsy" requested, the pathologist being under the impression that there has been a mix-up in specimens from the clinic. They are small, pedunculated adenomas composed of glandular cylindrical epithelium, and they may be multiple. They may also appear at the margins of epidermoid carcinomas, which will cause confusion.

LEIOMYOMAS, LIPOMAS, AND FIBROMAS have been reported in the esophagus, but are uncommon.

RHABDOMYOSARCOMA usually appears on the anterior wall of the organ in the form of a polypoid tumor. It is extremely rare and of the same freakish variety as those which are found in the uterus, vagina and prostate. Striated muscle in these situations is in the nature of a misplaced embryonal rest. Rhabdomyosarcoma is described and discussed at length in the chapter on Muscular Tissue.

CARCINOMA. This usually occurs at one of the points of normal constriction of the organ: the level of the cricoid cartilage, the bifurcation of the trachea, and the foramen in the diaphragm. The tumor may develop simultaneously in the lower third of the esophagus and in the cardia of the stomach. It tends to metastasize along the esophageal wall and to spread from this to the lymphatics. Men are affected in 75 per cent of the cases.

As is usual in the alimentary tract, three types of carcinoma may be recognized: flat and ulcerating, large and fungating, and infiltrating. Most of these are epidermoid carcinomas; there is one form of adenocarcinoma of the esophagus. The first form mentioned (flat and ulcerating) is usually an epidermoid carcinoma that exhibits cornification and formation of pearls and is derived from the epidermoid mucosa of the esophagus; the second (large and fungating) includes bulky epidermoid examples or adenocarcinoma derived from the adnexal mucous glands; the third, or infiltrating type, may be of a mature epidermoid

or more primitive plexiform nature—rarely a scirrhus adenocarcinoma is encountered. Carcinosarcoma has been described, but is exceedingly rare. One must carefully distinguish between the adenocarcinomas of the esophagus and those of the gastric cardia, which may grow upward into the esophagus. This is not always easy.



Somewhat plexiform and typical epidermoid carcinoma of esophagus. The black masses are bright red in the actual section and represent heavily keratinized epithelial "pearls"

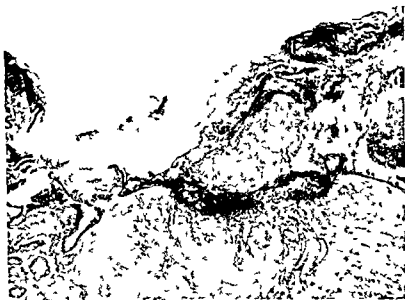
Ewing stresses an important feature of esophageal carcinoma: its tendency to cause very large metastases in the cervical chains of lymph nodes while, at the same time, the primary tumor is so small as to give no symptoms and to be discoverable only by means of esophagoscopy. Should one find metastases of epidermoid carcinoma in biopsies of cervical lymph nodes, without any evidence of oral carcinoma in the clinical history, one should suggest esophagoscopy. If nothing should be discovered there is the possibility of a primary tumor in the fossa of Rosenmüller in the pharynx.

Epidermoid carcinomas of the lower end of the esophagus may grow some distance into the cardia of the stomach, where they form infiltrating masses that might be mistaken for adenocarcinoma of the cardia. The microscopic sections will decide the

fibrin on the gastric surface and from the ultimate organization of this useful material

Ulcers, like similar lesions, heal by cicatrization of the defect and ultimate regeneration and closing over of the mucosa. This leaves a scar with a depressed pit over its mucous surface. Such scars may extend through all coats of the organ, and if they

tive appendicitis. This is known as "phlegmonous gastritis." The organ is much red dened, and its wall is thick and boggy, there may be fibrin on the serosa, while the mucosa (which is of an angry deep red) is swollen and may show ulceration. The process could result from spreading infection from an ulcer, or it may appear to be independent of any focal point of departure



Bed of minute peptic ulcer. Note denudation of mucosa and scab of coagulated blood overlying several dilated vessels in granulation tissue of bed.

are extensive enough they may cause contractions and deformities such as the "hour-glass stomach." In other cases outpocketings may occur, causing diverticula and gross distortions. Such lesions in the pyloric region may lead to considerable narrowing of the pyloric outlet as they heal, and true stenosis may result and, in turn, produce hypertrophy of the musculature of the antrum and pylorus, thus setting up a vicious circle.

Inflammation. The milder gastritides do not concern us here, as they are seldom surgical problems. Occasionally one finds an organ that has been subtotally resected for ulcer or carcinoma which turns out to be completely and acutely inflamed, very much as the appendix would be in acute suppu-

Microscopically the wall is found to be thronged with polymorphonuclear leukocytes and, to a lesser extent, by other cells common to inflammation. The vessels are engorged, and there may be hemorrhagic foci. The mucosa is partly destroyed and eroded, or it may merely be the site of an active inflammatory infiltration. Its goblet cells may show engorgement with mucus.

SPECIFIC LESIONS. Tuberculosis and syphilis have been reported as occurring in the stomach, but one so rarely finds either of them that they rapidly become somewhat mythical entities in the pathologist's range of experience. Nevertheless, they are infallibly mentioned in the textbooks. Tuberculosis takes the form of miliary lesions or tuberculous ulcers, while syphilis produces

cidedly vague but suggestive ideas. Exhausting disease, deficient diet, gastritis, and a neurotic temperament have all been cited without convincing us as to the validity of any one of them. Ulcer is more common in males in their thirties, females being attacked at an earlier age and less frequently.

CHRONIC PEPTIC ULCER. This is not really chronic in the sense of chronic inflammation, but represents a continuing acute ulcer so that it is essentially of the subacute variety. An ulcer that does not heal after the initial shallow and acute phase proceeds to undergo inflammatory changes and to penetrate more deeply into the gastric wall until it may perforate it; very often, it may develop more widely as well. At first circular or ovoid and "punched out," it may assume irregular outlines that are serpiginous; sometimes it may form a slit-like lesion that may almost encircle the pylorus. An ulcer of long standing may attain a diameter of 4 cm. or more, perforate slowly, and, if in contact with another organ such as the pancreas, present the denuded surface of that organ in its base.

The chronic ulcer is most usually seen in the neighborhood of the pylorus or along the lesser curvature (the "Magenstrasse" of the German literature). Aschoff called attention to the "terracing" or step-like appearance of the margin of the ulcer, which looks as though smaller and smaller circles of tissue have been destroyed in successive layers as the ulcer has worked its way through the wall. Should the ulcer persist, there is swelling of the margin which may overhang the rim of the excavation and present an undermined appearance. As this is more common in carcinoma it may be confusing in differentiating the ulcers from carcinomatous lesions. A section through such an ulcer reveals a base to the crater that resembles brown paper, and beneath this a mass of cicatricial tissue fades into the neighboring wall; a section through a carcinomatous ulcer of corresponding size usually reveals a granular, gray base, a millimeter or two in thickness, fading into

the underlying scar. The wall of a chronic ulcer is hard and indurated, but not stony hard as in carcinoma, and its margin usually fails to burgeon into the frill-like or coxcomb-like thickening that is almost pathognomonic of carcinoma.

In microscopic sagittal sections these subacute ulcers show a cup-like depression that is covered by a slough. Beneath this there is a layer of vascular granulation tissue, and next in turn a layer of scar tissue that has more or less completely replaced the underlying muscle. This scar is filled with inflammatory cells among which plasma cells and eosinophils attest to the subacute nature of the inflammation. The former often contain Russell bodies. Very occasionally macrophages (which naturally abound in such lesions) may be observed to be filled with broken-down collagenous material; these are found near the margin of the lesion. Where mucosa forms the rim of the ulcer it is apt to be hypertrophic, its cells engorged with mucus, and its architecture obscured by an inflammatory reaction. The blood vessels almost invariably show sclerosis and evidence of antecedent thrombosis—a fact that is utilized by proponents of the vascular theories as to etiology. As similar vascular lesions are common in chronic cholecystitis and in appendices that have been repeatedly inflamed, this may be a result rather than a cause of the process. There are also acute lesions in the vessels and nerves that are involved in the inflammatory reaction; thus angiitis, thrombosis, periangiitis, and perineuritis develop near the ulcer.

The common complications are: (1) hemorrhage from erosion of vessels in the bed of the ulcer, and (2) perforation. The latter may occur rapidly, voiding gastric contents and blood into the peritoneal cavity, with consequent peritonitis; or it may be more gradual and become walled off by omentum or adhesions between the stomach and neighboring viscera. In that case peritonitis, if it develops, is a strictly local affair. The adhesions result from deposition of

papillary structure is the rule, but mitotic figures and invasion of the base of the tumor are wanting. Such tumors are readily removed by a simple operation that spares the pylorus.

GASTRIC CARCINOMA Generally speaking, the management of gastric carcinoma is handicapped by the fact that most of the patients are sent to the surgeon after the lesion has become well established and quite

ritation should be taken into account. One who peruses the probable etiologic factors (particularly the dietary ones) advanced in the literature is likely to become completely confused, as authorities disagree violently on the influence of food, heat, alcohol, tobacco, and the like. That chronic ulcers may become malignant is true in about 10 per cent of the cases, but the very high figures of the Mayo Clinic are based upon the recognition of individual cancer cells, rather than on over all pictures of the lesions; this makes its claim that 71 per cent of cancers are associated with gastric ulcer too high to pass unchallenged.

Gastric carcinoma may be classified in a number of ways, and most of them will be found to confuse the subject, rather than to clarify it, possibly the gross appearance and general habitus of these tumors affords the simplest basis for classification. Thus they may be (1) fungating and bulky, growing out into the lumen rather than burrowing into the wall, (2) flat, spreading, and infiltrating, or (3) inconspicuous on the mucosal surface and very desmoplastic, causing fibrosis of the wall about them (scirrhous type). Subdivisions of these groups may be made on the basis of their microscopic appearance, but a too slavish adherence to this will lead into a maze of probably unessential details.

FUNGATING TYPE This type may occur anywhere in the organ, but shows a predilection for the pylorus. It is essentially a malignant adenoma and is made up of large bulbous lobes that project a centimeter or so above the adjacent mucosa and become necrotic and ulcerated with consequent mixed infection, sloughs, and hemorrhage. It may begin as a polypoid tumor—a type more or less common to all segments of the alimentary canal. Microscopically it is apt to be composed of adenomatous overgrowths of the covering layer of mucosal epithelium. There are many papillae composed of atypical epithelial cells supported on a central core of stroma. In some instances it produces large amounts of mucus



Well differentiated papillary adenoma of pylorus ("pyloric polyp")

large, it may even have invaded the stomach widely and metastasized to its lymphatics. In spite of x-ray evidence to reinforce clinical signs of postprandial distress and achlorhydria, even despite the presence of a palpable mass in the region of the stomach, the patient will be treated expectantly and not sent to the surgeon until it is too late for complete eradication of the growth and its metastases. This necessarily makes for a poor prognosis.

Carcinoma of the stomach lends the list in frequency in the case of men, just as carcinoma of the uterus is the most common in women, the ratio for gastric cancer is about 35 women to 65 men. It is a disease of later life, the average age incidence being about the sixtieth year, although it may come earlier. It appears to represent a familial predisposition. Trauma is of little importance in its etiology, but chronic ir-

gastric gummas and occasionally a diffuse nodular infiltration or a chronic fibrotic lesion.

CHRONIC GASTRITIS. The atrophic and hypertrophic forms of this lesion are more or less on a par with the renal lesions that used to be known as "nephritis" and are now called "nephrosis." In the atrophic form there is a definite thinning out of the mucosa and atrophy of the muscular coats without much that would, under the microscope, justify the termination "itis." It is said that there is a marked diminution in the number of argentaffin Kulschitzky cells. In the hypertrophic form there is engorgement of the mucosa, which becomes reddened and swollen and covered with a mass of mucus; the rugae are swollen and heavy. These factors cause barium to adhere to the wall in a characteristically reticulated pattern that is clearly visible and diagnosable on x-ray examination.

Microscopically one finds an infiltration of the tunica propria by plasma cells, eosinophils, and lymphocytes, but the picture is not so much that of inflammation as it is of hyperplasia. These two lesions are of importance in surgical pathology only in so far as they may or may not have a bearing upon the causation of carcinoma. Surgical pathologists attempting to evaluate this had better make sure of their criteria before pronouncing the mucosa in the vicinity of a cancer to represent either hypertrophic or atrophic gastritis.

CHRONIC DIFFUSE GASTRITIS. There is some question as to whether this condition (formerly known as "linitis plastica") can exist independently of the presence of the diffuse scirrhous carcinoma that now goes under that name. Presumably there may be a diffuse infiltrative chronic inflammation of the gastric wall, and it sometimes happens that one is tempted to consider this as an independent condition unconnected with carcinoma. The picture is essentially the same, except that the inflammatory infiltrate must totally lack neoplastic cells. The suspicion always arises, then, that these

have been overlooked, and textbooks are always very guarded in stating that there can exist a noncancerous form of linitis plastica. In twelve years' experience with the surgical material in a large hospital only one such example has come to light in which careful microscopic examination failed to show carcinomatous cells present somewhere in the section.

Gastric Tumors. As the stomach is composed of muscle, mucous membrane of a variable histologic type, and the usual supporting structures of connective tissue, fat, and vascular and nervous trunks, these will be the possible sites of tumors. Among them the mucosa comes first, next the muscle, and finally the fatty, nervous, and fibrous elements in about that order of frequency.

ADENOMA. This is the "gastric polyp" of surgical literature; it is a nonmalignant adenoma that is usually pedunculated, although it can be diffuse and sessile. Such tumors usually occur in the neighborhood of the pylorus, where they have the disconcerting habit of being forced into its opening by a peristaltic wave and staying there in the embrace of the sphincter for some time before the sphincter relaxes and allows the polyp to pop back into the antrum. During this time there has been pylorospasm and great distress to the patient, possibly with attendant nausea and vomiting. As a result of this massaging by the sphincter, these adenomas may become traumatized and bleed extensively through surprisingly trifling ulcerations on the surface. For the same reason their pedicles may become elongated to several centimeters. Polyps may occasionally be multiple and small; the sessile type of tumor is essentially a "polyp patch" in the pylorus, an irregular area several centimeters in diameter and studded with small polyps of a few millimeters in diameter.

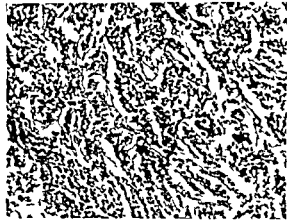
Gastric adenoma usually exhibits the microscopic architecture of pyloric mucosa with a great deal of exuberant epithelium arranged in a comparatively orderly fashion, but extremely redundant and papillary;

which, as it accumulates in those acini which do not empty onto the surface, gradually ruptures their walls and results in the production of lakes of mucus in which groups of epithelial cells float about. The walls of these spaces may or may not retain some epithelial lining. Many of the cells accumulate mucus in their cytoplasm and become "signet ring cells" with their nuclei displaced to one side and the cytoplasm thinned out into a delicate envelope. Such cells are more numerous in the more diffuse forms of this tumor and may become so dissociated from one another as to suggest an exudate in the base of the neoplasm. They may metastasize to the ovary, where they produce the so called "Krukenberg tumor," which will be discussed in the proper place in a later chapter. Metastasis with these tumors occurs somewhat later than it does in those we are about to consider.

FLAT AND INFILTRATING TYPE Carcinoma Developing in Gastric Ulcer As has been said, about 10 per cent of gastric tumors develop in long standing chronic ulcers, usually arising in the margin of these in one quadrant or another. They exhibit a flat, spreading growth that tends to infiltrate the lip of the ulcer and to form an everted, thickened ring that radiates into the surrounding wall. They occur where ulcers are most common. It is very difficult to detect them on macroscopic examination, one finds a small ulcer with an eroded, raw base showing a suggestive nodular thickening of a portion of its rim that becomes undermined, overhanging, and hard. Some times this appears to be explicable on the basis of induration from inflammation, and the presence of carcinoma is proved only by microscopic inspection. Such tumors show branching cords of small, atypical cells that infiltrate the margin of the lesion, which otherwise has the characteristics of an ordinary peptic ulcer. They will be found penetrating the scar tissue at the base and may roam to some distance from the ulcer's site. They are apt to be rather nondescript

in their appearance and to give little clue as to exactly which layer of the mucosa gave them origin.

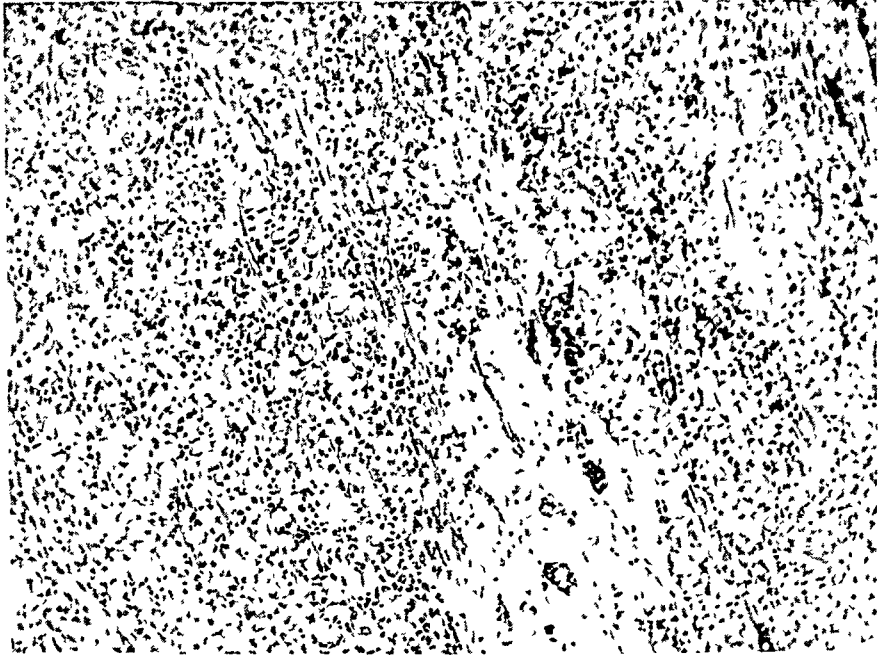
Developing as Primary Carcinoma This type begins as a button like lesion in the mucosa, growing outward into the lumen in the form of a somewhat cupped mushroom like excrescence as it develops and, at the same time, invading the underlying wall. After it has reached a certain size it tends



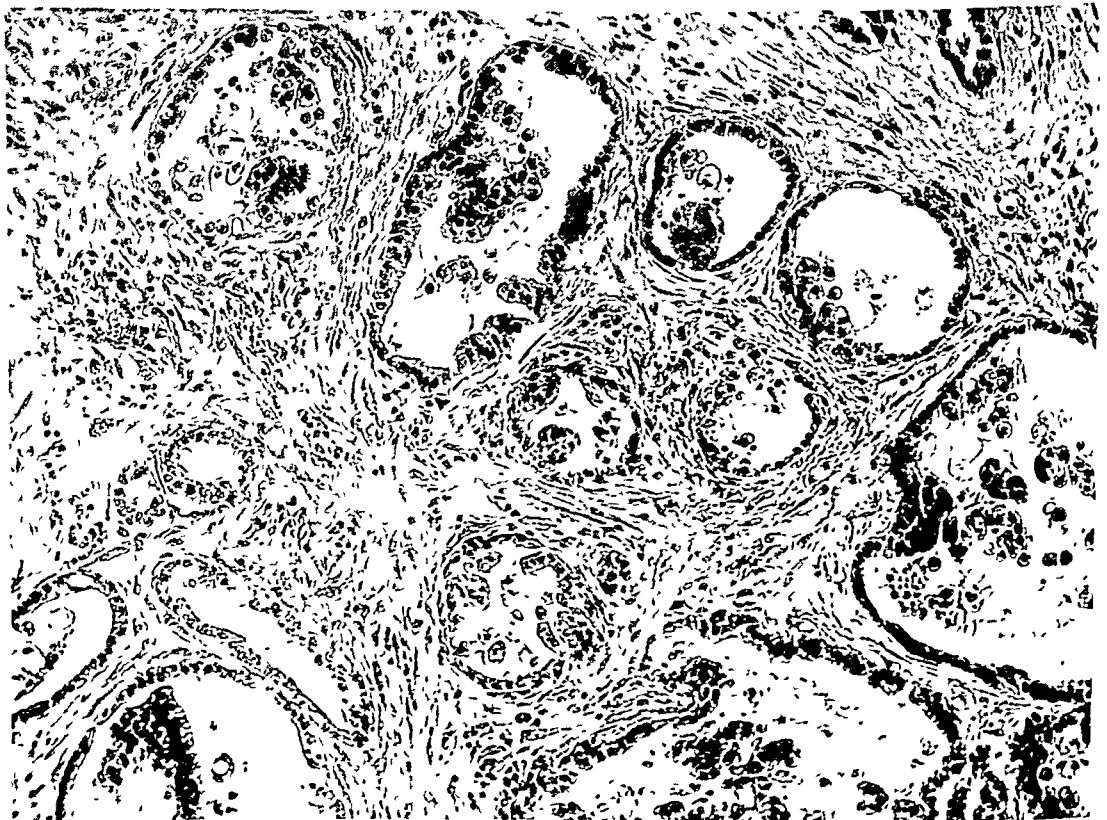
Small celled carcinoma of pylorus. It resembles retothelial sarcoma in appearance, but the reticulum forms basement membranes about groups of cells which it does not penetrate. In sarcoma it would be intimately intermingled with them throughout the masses.

to ulcerate at its center, becoming crateriform with serpiginous, scalloped margins that are like a cocomb and extremely firm. The base of the ulcer, instead of being raw, with terraced edges and the outline of muscle in its base, is covered by apparently normal epithelium, so that it may have the appearance of having healed over. This is not so, however, as the carcinoma is epithelial and its surface therefore looks like that tissue. This type occurs in any part of the organ but shows a preference for the fundus and cardia, often developing along the lesser curvature and extending down the anterior and posterior walls for a considerable distance. It metastasizes early to the regional lymph nodes.

Microscopically it may exhibit a variety of forms of epithelium, this may be of



Mucous carcinoma of stomach "in situ." Note signet-ring cells that compose tumor; they are arranged within normal frame of gastric mucosa without distorting it—hence the term "in situ."



Section from omentum showing massive metastasis from gastric adenocarcinoma of mucous variety.

one can trace the progress of the growth from areas of metaplasia in the mucosa. Fibrosis is marked and the tumor is involved in dense bands of connective tissue.

Linitis Plastica This type of scirrhous carcinoma involves the entire wall of the stomach and shows little in the way of a primary lesion in the mucosa. Sometimes it is impossible to detect much change in the thickened and nodular membrane that



Infiltration of gastric musculature by scirrhous carcinoma in linitis plastica or 'leather bottle stomach'. Note neoplastic cells embedded in muscular bundles and disrupting these.

lines the organ, while the wall is converted into an inflexible, leathery structure that well merits the popular name 'leather bottle'. Microscopically one finds a gastric wall that is criss-crossed by fibrous bands of connective tissue containing very widely and sparsely scattered cords of small cells that might mislead one into thinking them to be macrophages. Often they are more easily found in the muscular coats than in the edematous and very fibrous submucosa. A stain for mucus will demonstrate some mucus in their cytoplasm, and by careful search among the muscular bundles one may find small acini of metaplastic epithelium. This form of scirrhous carcinoma does not metastasize rapidly and it may form foci of fibrotic tumor growth on the serosa of the stomach and of neighboring viscera.

TREATMENT OF GASTRIC CARCINOMA The most important factor in the treatment of gastric cancer is early diagnosis and prompt recognition; otherwise it will be too late for surgical extirpation of the tumor-bearing segment of the organ. Irradiation is of palliative value only. Naturally there should be wide excision (total gastrectomy, if necessary), and resection of the tumorous segment should always be as thorough and wide as possible. This enables the surgeon to remove a large part of the gastrohepatic and gastrocolic omenta with the lymph nodes that they contain.

Tumors of Gastric Muscle LEIOMYOMA Nonmalignant muscular tumors of the wall of the stomach are far more common than is currently supposed, but even so they constitute but a small percentage of all gastric neoplasms, most of which are malignant and epithelial. They are found in the wall as light brown fairly well-circumscribed neoplasms that are more or less spherical or ovoid and tend to develop just beneath the mucosa, which they elevate. They may cause obstruction of the pyloric ring. It is quite unusual to discover in the overlying mucosa a tiny, punched-out ulcer, measuring only a few millimeters in diameter, from which copious hemorrhages may take place and lead to a diagnosis of gastric ulcer or carcinoma. The x-ray, however, fails to reveal them clearly, so that there is always some argument between clinicians and roentgenologists as to the nature of the lesion. (See illustration of leiomyoma of gastric wall in Chapter 7.)

Microscopically the tumors appear exactly like those of the uterus and prostate, but they tend to be a little more purely muscular and less fibrous than those of the uterus. Some of them may show very immature myocytes, these are short, plump spindle cells with a sarcoplasm that stains brilliant red with the Masson trichrome technic and shows sheaths of reticulum fibers in silver impregnations, which are useful in diagnosing them. Mitoses do not present and their histology is very orderly.

the "covering" or superficial variety; it may be derived from the long gastric glands and composed of small, cuboidal cells; or it may become dedifferentiated and its cells lie so discretely separated from one another that they resemble lymphocytes and are apt to lead to a mistaken diagnosis of lymphosarcoma. Such a form is the "diffuse small-

distorted, or contracted tissue that tends to contract on its outer surface when the stomach is cut open, leaving the mucosal surface convex, while the serosal surface becomes concave. There are two types which seem to be sufficiently different to warrant separating them: the pyloric scirrhus carcinoma and the diffuse scirrhus carcinoma



Specimen of "leather-bottle stomach" or "linitis plastica," a form of diffuse scirrhus carcinoma. Thickened walls and rugae speak for themselves. (Army Medical Museum 64450.)

celled carcinoma," which is naturally very malignant. Tumors composed of eosinophile parietal cells are not encountered; most of the neoplasms arise in chief cells of the gastric glands. They are found penetrating the entire wall of the organ and spreading out underneath the serosa. As they are a very malignant group metastases from these tumors may spread beyond the regional lymph nodes to the liver.

SCIRRHUS OR FIBROSING TYPE This carcinoma occasions a lively overgrowth of fibrous connective tissue and is very diffuse, so that the lesion on the mucosa may be very inconspicuous and consist of apparently submucosal nodules that are stony hard. It converts the wall into a leathery,

or "linitis plastica" (leather-bottle stomach).

Pyloric Scirrhus Carcinoma. There may be some nodular thickening of the mucosa in the pyloric region, but the tumor grows in a deep, infiltrating fashion that narrows the pylorus. There may be slight mucosal erosion, but ulceration is uncommon and not prominent. Fairly small lesions of this type give rise to early and massive metastasis in neighboring organs such as the liver—daughter growths that may outstrip the primary lesion and grow to many times its size. Microscopically one finds infiltrating chains of cells that tend to form small complexes of adenocarcinoma among the fibers of the muscularis; there may be spots where

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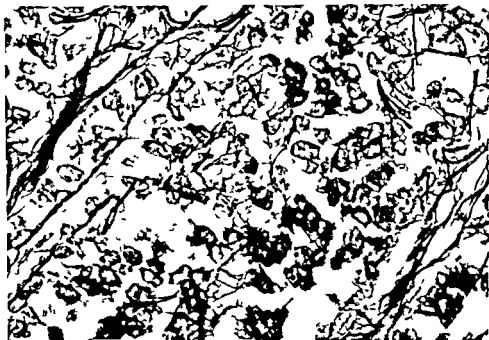
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phosarcoma. One of the Romanowsky stains, like Giemsa's, together with a mucicarmine stain should be sufficient to bring a clean cut decision, the Romanowsky stains are excellent for demonstrating the morphology of lymphoblasts and lymphocytes, with their azurophil granules, while the mucicarmine stain, should it reveal intracellular mucus, would rule out lymphoid



Section impregnated with silver and taken from retothelial sarcoma of stomach. There is very intimate relationship of cells to reticular stroma, which is nowhere forming "basement membranes."

lymphosarcomas and need no special description (see Lymphosarcoma in Chapter 11). Unlike most of these, however, they show a rather low grade of malignant growth and, once removed, have been known to cause no further symptoms over a period of 15 years or more. This refers to solitary examples in the stomach, if lymphosarcoma exists elsewhere in the body as well the prognosis is grave, for the problem is one of a unit in a complex of tumors, rather than a solitary example.

The pathologist should make careful investigation of such tumors to rule out small celled diffuse carcinoma, which is commonly found in the same situation and has a close superficial microscopic resemblance to lym-

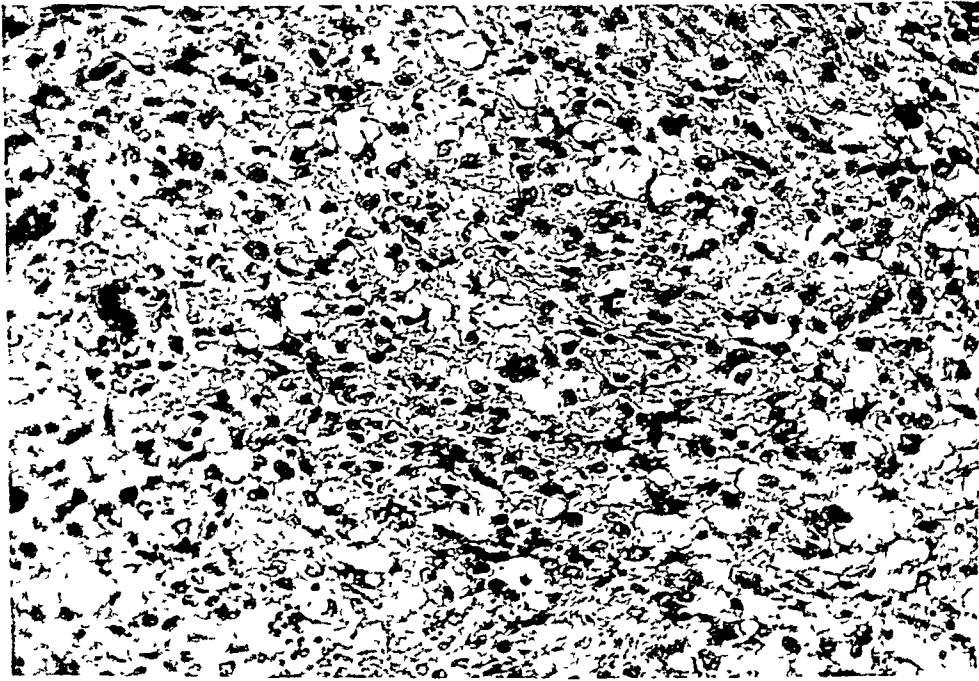
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While x-ray irradiation will temporarily "knock down" lymphosarcomas, it seldom cures them, surgery, however, has had such good results on the few cases we have observed or of which we have personal knowledge that it seems preferable to the uncertainties of irradiation.

LIPOMA. Lipomas of the stomach are small, may arise in the submucosa, and are so infrequently found that they are of relatively little importance. Their malignant form has been reported in the stomach, but this is of academic interest only.

LEIOMYOSARCOMA. Leiomyosarcoma of the stomach is a very insidious growth that usually lurks in the cardia and, for that reason, occupies a "blind" or "silent" area, both because it may lie behind the lens of a gastroscope and not be seen and because it does not interfere with gastric secretion and therefore fails to produce any symptoms other than hemorrhage, which may

more or less fusiform, have large and hyperchromatic nuclei, and show coarse myogial fibrils running parallel with the longitudinal axis of the cell within its cytoplasm. Mitoses are numerous and may be very atypical. Another form of the tumor exhibits rounded cells that are much less suggestive of muscular origin. In both types there may be some attempt at muscular architecture, with



Leiomyosarcoma of gastric muscularis. This is a very loosely woven tumor that might easily be mistaken for liposarcoma in this instance. Special stains failed to demonstrate fat and showed characteristically reddish-orange sarcoplasm in cellular elements.

be copious and has its origin in small ulcers like those described in the case of the non-malignant leiomyoma. This growth becomes bulky and of a lightish brown, and may resemble smooth muscle, if it is pale and granular, however (as it sometimes is in the more malignant varieties), it may be mistaken for carcinoma. Careful gross examination will demonstrate that it is usually covered by a thin, normal-looking mucosa and that it occupies the muscular coat of the organ.

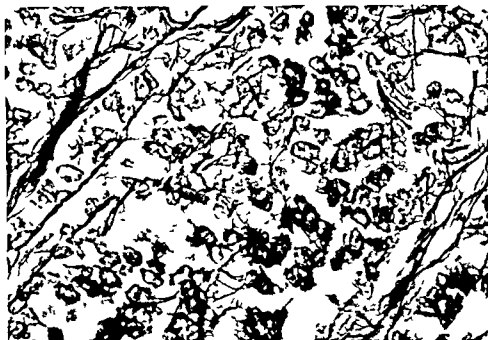
Microscopically its picture varies: some of the paler tumors are composed of very bizarre cells that may resemble epithelium sufficiently to lead to a false diagnosis even by experienced pathologists. The cells are

the cells forming bands like those of smooth muscle; this is particularly true of the better differentiated examples. Masson's stain and silver impregnation are valuable in identifying the tissue, for the brilliant reds of the former show small polar collections of sarcoplasm like that of myocytes, while the silver demonstrates parallel fibers of reticulum which, in normal muscle, constitute the sheaths of the cells. In these tumors special techniques are more necessary than usual before their nature can be satisfactorily demonstrated. As to treatment, surgery is again indicated.

LYMPHOSARCOMA. Nonmalignant tumors of lymphoid tissue in the stomach are not described, but sarcomas are occasionally en-

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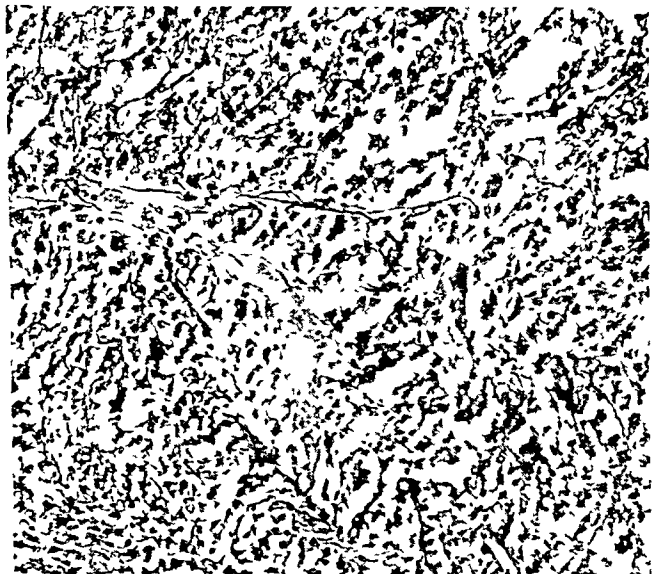
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FIBROMA. Fibroma and fibrosarcoma are not at all common, though they may arise in the connective tissue of the stomach.

NEUROGENOUS TUMORS. Two French observers have stated that practically all of the tumors of the alimentary tract commonly attributed to neoplasia of muscular tissue are, in reality, of nervous origin. This statement should be carefully checked over before the reader puts too much reliance



Retothelial sarcoma of stomach impregnated with silver to demonstrate delicate reticulum.

upon it; nervous tumors are fairly easy to recognize, and as there is ample nervous tissue in the gastric wall it is possible that one might find neurilemmomas, neurofibromas, and even neurogenous sarcomas in that situation. Although we have been on the lookout for such tumors during the past decade, none has come our way.

DUODENUM

This segment of the alimentary tract presents one of the most fertile fields for surgery on account of the fact that ulcers very commonly develop here, but it also presents inexplicably sterile ground for the "tumor pathologist" or "oncologist," as tumors appear to shun this region to a notable degree.

Duodenal Ulcer. Duodenal ulcers do not differ materially from ulcers of the pylorus; some of them straddle the pyloric orifice

and lie partly in one organ, partly in the other. They follow the same general course as that pursued by their gastric relatives, and they may do almost everything that these do, except that they very rarely become carcinomatous. Ewing, reporting the recording of ten cases up to 1940, said that he had seen one that was questionable and another that was part of a pyloric carcinoma that extended down into the duodenum.

Ulcers usually arise in the first part of the duodenal loop. Duodenal ulcers may perforate into neighboring organs or into the peritoneal cavity, they may bleed copiously, become subacute, and continue for some time; and when they are acutely inflamed they may involve the neighboring tissues in acute inflammation. Such a condition, in the head of the pancreas, may occasion swelling and induration of that organ and be mistaken for pancreatic carcinoma at operation. It will cause many of the symptoms of that disease by obstructing the flow of bile through the papilla of Vater.

Diverticula. The duodenum may be the site of diverticula, which in this situation are usually the outcome of healed ulcers, although they may result from congenital defects. They are rarely of much importance.

Tumors. ADENOMA. Nonmalignant adenoma of the duodenum may occasionally be met with, taking the form of multiple small polyps.

CARCINOMA. Carcinoma of the duodenum comprises about 5 per cent of the total number of intestinal carcinomas, but one rarely encounters it. When found it shows a predilection for the region of the papilla of Vater, and in this situation it must be identified as definitely of duodenal origin before a diagnosis is issued, because carcinomas of the common duct and ampulla just as frequently invade the papilla. Thus a carcinoma in this situation might indicate one originating in the common duct and spreading downward. Duodenal carcinoma

usually afflicts elderly subjects in the sixth decade, this is in sharp contrast with that of the colon, for example, where young adults often harbor malignant tumors. It occurs in the upper, second, and third portions of the duodenum in the ratio of approximately 5:25:4, respectively. That of the upper segment is usually the result of carcinomatous transformation in a duodenal ulcer. That of the second segment is situated around the papilla of Vater, where it begins as a papillary growth that surrounds that orifice and causes biliary obstruction. Even partial obstruction may occasion great dilatation of the common duct, working back into its feeders from the liver and pancreas. Carcinoma of the third portion of the duodenum is so rare as to be practically nonexistent in the everyday practice of a large hospital, it has more in common with the preceding type than with that in the first segment. When it is seen it is either broad and ulcerating or bulky and fungating, both types may cause obstruction and dilatation of the duodenum and stomach if there is much cicatricial contracture.

Microscopically, these tumors resemble the duodenal mucosa to a large degree, some of them suggesting origin in Brunner's glands, others looking more like the covering layer of the mucosa. If a duodenal carcinoma does not suggest this architecture, but grows as a complex of more or less duct-like structures composed of metaplastic epithelium with a definite resemblance to that of normal bile ducts, it probably represents a spread into the duodenum of a carcinoma originating in the bile duct. This type is apt to be sharply localized about the papilla of Vater and to spread up the common duct, while the duodenal type grows primarily along the surface of the mucosa, and while it surrounds and obstructs the papilla it does not tend to ascend within its lumen. The histology of tumors of the third portion of the duodenum approaches the type that is common to the intestines as a whole,

largely composed of simple glandular epithelium resembling that which covers the intestinal mucosal surface.

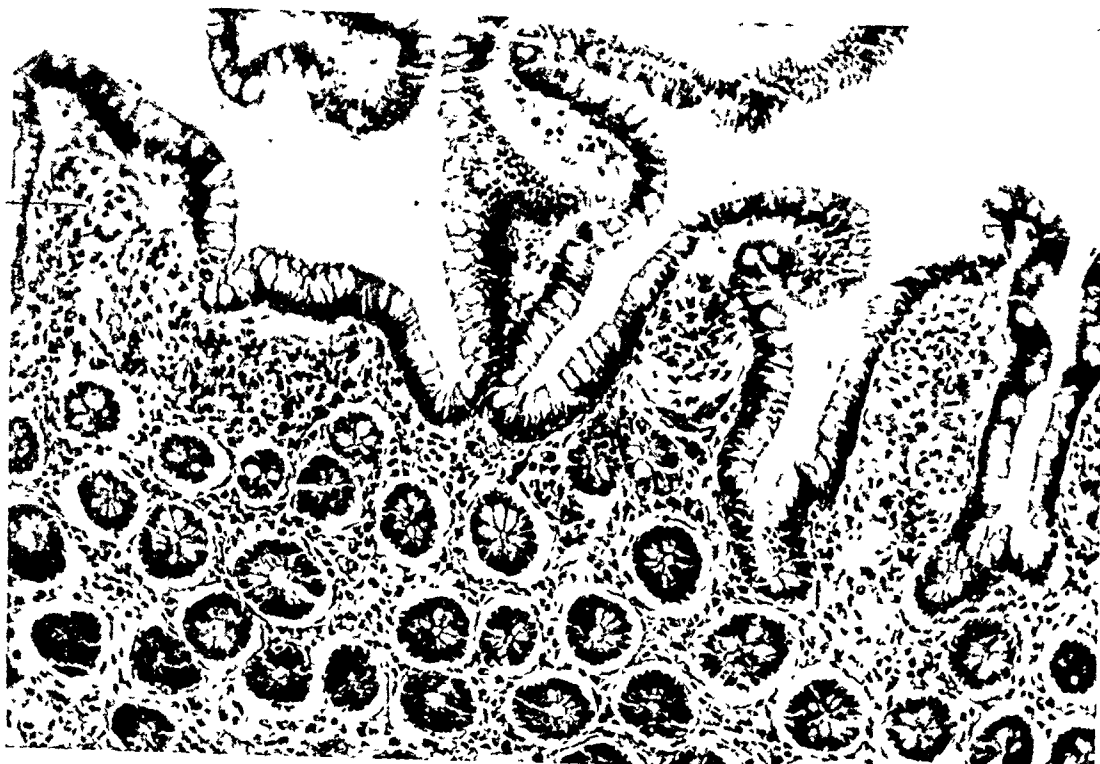
SMALL INTESTINE

The jejunum and ileum differ chiefly in that the former has a more rugose, valvular mucosa and lacks the lymphoid tissue which is present in the Peyer's patches of the ileum—a segment that is smoother and less prominently ringed with valvulae conniventes than is its predecessor.

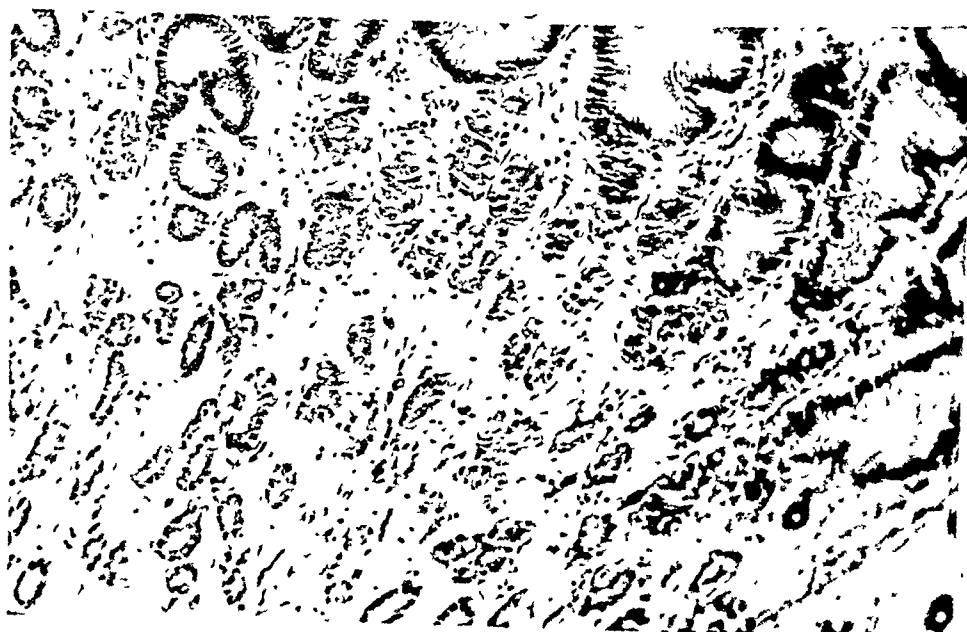
Ulcer. The jejunum is of interest chiefly in connection with marginal ulcers that occur about the stomas of gastrojejunostomies slitlike, raw areas rimming the stoma and giving rise to considerable and stubborn hemorrhages which necessitate the dismantling of the gastrojejunostomy. Microscopically these ulcers are very annoying problems, for it is always difficult to obtain good sections that maintain the relations of the stomach and jejunum in readily recognizable form. They are shallow and resemble peptic ulcers in their histology.

Anomalies. **MECKEL'S DIVERTICULUM.** Probably the commonest intestinal anomaly is the presence in the ileum of a diverticulum at a point about one meter from the ileocecal valve. This is the proximal remnant of the omphalomesenteric duct that takes the form of a finger-like pouch projecting from the ileum. It may be a mere bud a centimeter or so in length, or it may extend several centimeters beyond the gut and attain a caliber commensurate with that of the ileum. If the diverticulum is long and well developed it usually possesses a mesentery of its own.

Some of these diverticula show mucosa typical of the ileum or the jejunum or even the duodenum, others present areas of thicker and whiter mucosa near their fundi, and in these areas gastric glands will be found on microscopic examination, a few of them may show pancreatic or embryonic glandular tissue with small cysts. The fundus may present a canal through the umbilicus, but usually it is blind and may be



Intestinal mucosa lining a Meckel's diverticulum that is uninfamed.



Gastric mucosa from fundus of a Meckel's diverticulum in which a typical peptic ulcer had developed and bled copiously.

connected with the abdominal wall by a strand of vascular connective tissue, or it may have a rounded and smooth extremity without any such connection. If the connection is present, however, it may give rise to strangulation of loops of intestine that become entangled with it and become so twisted that their blood supply is cut off. Severe hemorrhage occurs when gastric

Vascular Disturbances As the intestinal arteries are terminal vessels, anything that interferes with their circulation will lead to infarction of long segments of intestine at the end of the mesenteric fan that supplies them, this results in gangrene. Infarction may be simply a matter of mechanical compression of vessels, or it may be a mixture of obstruction by embolic or throm-



Intestinal mucosa in acutely inflamed and partially gangrenous Meckel's diverticulum. There is a mass of fibrin over mucosa at upper right.

mucosa is contained in these diverticula, and this bleeding always leads one to suspect that such tissue may be found in the sac once the diverticulum is removed.

Occasionally a Meckel's diverticulum may become acutely inflamed, just as would an appendix, and acute Meckel's diverticulitis results. This may go on to a suppurative form, with abscesses in a thickened and angry red wall that is covered with fibrin, and it may involve the neighboring wall of the ileum. This, in turn, may proceed to gangrene and perforation.

OTHER DIVERTICULA Structures similar to the diverticula of the duodenum occasionally arise in the small intestine and project into its mesentery.

botic plugs in these—plugs that may already be filled with bacterial colonies and lead to infection in addition to this mechanical obstruction. As a result, the affected intestinal segment undergoes acute inflammation and necrosis which may progress rapidly, at first reddened and edematous, the inflammatory reaction is succeeded by necrosis or gangrene, and the organ becomes greenish gray and then almost black, its wall toneless and thin. It then takes on a characteristic fishy odor that is unmistakable once it has been smelt. During this process there may be deposits of considerable fibrin along the affected segment.

Microscopically one finds the expected changes that go with inflammation and ne-

crisis, but it is remarkable how often an intestinal wall that seemed completely necrotic on macroscopic examination and was undoubtedly not viable (inasmuch as it would not resume function when replaced in the peritoneal cavity) will appear to be fairly well preserved when viewed through the microscope. Much of this appearance depends upon the segment from which the section was taken, so that one must always choose the worst possible part of the gross specimen for microscopic examination; otherwise one may be misled into believing that conditions are not as bad as the surgeon thought they were.

There are several reasons for vascular occlusion in the intestine; that they are mechanical and inflammatory has been indicated.

VOLVULUS. This literally means "a twisting"; the intestine, in the course of peristalsis, may become twisted upon its mesentery as a pedicle or axis, and its supply of blood may thus be shut off. Or it may, during vigorous contractions, penetrate between adhesions from some previous inflammatory lesion and become imprisoned and unable to extricate itself. We have considered a similar accident in connection with the vestigial cord of a Meckel's diverticulum.

STRANGULATION. This somewhat resembles volvulus; a loop of intestine may work its way into a hernial sac, more and more of it passing through the neck of that structure until it becomes edematous and hyperemic, with consequent swelling that prevents its return to the abdominal cavity. When thus incarcerated its blood vessels are constricted and the circulation cut off. This may happen in the case of inguinal, femoral, ventral, and diaphragmatic hernias.

INTUSSUSCEPTION. Usually in the case of children a given length of intestine (the "intussusciens") will literally swallow part of the tract just proximal to it by a process of telescoping. In this the "swallowed" portion (the "intussusceptum") is drawn down within the intussusciens until

it can go no further on account of traction upon its mesentery. Naturally the combination of traction and compression effectively shuts off all circulation to the intussusceptum, which becomes necrotic and may slough off and be passed per rectum, while the upper end of the intussusciens becomes firmly united with the lower end of unaffected bowel just at the point of telescoping. This accomplishes a spontaneous end-to-end anastomosis.

Such an outcome may be prevented by prompt surgical intervention in which the intussusceptum is withdrawn from the intussusciens and anchored to some convenient point after the surgeon has assured himself that it is still viable. It goes almost without saying that a spontaneous cure, such as that just described, is more often an exception than it is the rule; the patient dies of shock if surgical intervention is not resorted to. The process is most frequently seen in the ascending colon of children, with the ileum being drawn into that organ.

Although in children intussusception is usually spontaneous, in adults it may result from the presence of a polypoid tumor bulky enough to form a mass similar to a bolus of food or feces which may be grasped in the peristaltic embrace of the lower segment.

Inflammation (Enteritis). Of the various forms of enteritis only a few present surgical problems.

ACUTE INFLAMMATION. Typhoid Fever. This disease, which is now rare although it used to be a veritable scourge, causes ulceration of the Peyer's patches of the ileum. These become reddened and swollen, ulcerating and giving origin to copious hemorrhages. If the process continues the ulcers may perforate, discharging intestinal contents into the peritoneal cavity. Such an event naturally calls for prompt surgical intervention.

The microscopic appearance of the lesion is striking and more or less unique. There is an enormous increase in the number of reticulo-endothelial cells of the Peyer's

patches until they completely obscure the histology of the lymphoid tissue. At the same time they phagocytose large numbers of lymphocytes, one phagocyte containing many of these in its cytoplasm. This results in mass necrosis of the patch and ulceration. In very severe cases lesions may be found outside of the Peyer's patches in the

terminal segment just proximal to the ileocecal valve, so that the disease is often called "terminal ileitis." "Regional ileitis" is a better name for reasons that will become obvious. It has been recognized for a comparatively short time since Crohn and his collaborators put it upon a firm clinico-pathologic basis. Very little progress has



Longitudinal section of shallow ulcer in regional ileitis. In this case there was also extensive involvement of colon. Bed of ulcer is coated with pus, fibrin, and debris. A solitary follicle is seen at left and epithelial rim of ulcer at right.

solitary lymph follicles of other parts of the intestinal tract. The enlarged mesenteric lymph nodes will exhibit exactly similar histologic pictures.

With proper supervision of the water supply and of sewage disposal, together with prophylactic vaccination, typhoid fever is now seldom encountered in modern cities. It may still crop up, however, in unenlightened communities where pollution of drinking water exists.

Regional Enteritis. This condition affects the small and large intestines alike, although its point of predilection is the ileum and, more particularly, the ileum's

been made in connection with its etiology, we know what it is rather than why. It occurs in young adults and runs a surprisingly slow and chronic clinical course in view of the intensely acute inflammation it may reveal in sections. It is clinically recognized by its long continued diarrheal symptoms and the characteristic picture it presents on x-ray examination. The intestine seems like a rubber hose in its affected segment, the barium forms a cylindrical cast surrounded by a lighter shadow of straight and thickened wall that seems to be inflexible.

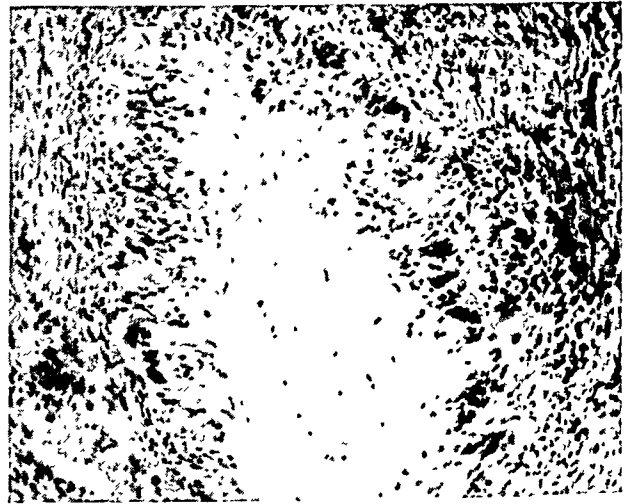
The pathologic picture, after such a seg-

ment has been surgically resected, is very typical: the wall is thick and brawny, reddened and inflamed, and there may be some patches of fibrin on its serosa. Upon being cut open the bowel is seen to have a characteristically altered mucosa which is a bright, angry red; it has been smoothed out by the underlying edema, exudate, and fibrosis that seem to proceed almost *pari passu*. On the mucosal surface there are sunken scars that run capricious courses and ulcers that vary from circular and rather ordinary shallow lesions to the almost pathognomonic longitudinal fissured ulcers that represent elongated slits in the mucosa covered with whitish slough and fibrin. Large ulcers with serpiginous borders may also be observed. The muscular wall is edematous and usually rubbery on palpation. In advanced cases there may be perforations and fistulous tracts penetrating the abdominal wall, or merely establishing fistulae between adjacent loops of intestine, such as ileum and ascending colon.

Microscopically one is immediately struck by two facts: the mucosa shows a patchy and intensely acute inflammation that seems to be quite disproportionate to the symptoms; and in the outer part of the wall, among the muscular layers or near them, there are tubercles that closely resemble those of tuberculosis. It is probable that many of the cases formerly reported as "chronic fibrous" or "plastic" tuberculosis of the intestine, more particularly of the colon, were really instances of regional enteritis. The tubercles are composed of epithelioid cells and giant cells that often contain crystalloid material in vacuoles. Tubercle bacilli are not demonstrable and there is no caseation in the tubercles. Boeck's sarcoid has been considered as a possible factor, but the idea has not gained any notable ground. It is conceivable that material from the inflamed and scarred mucosa is passed through the wall into the lymphatics, where it excites this tubercular, foreign-body reaction. Fatty substances may play a conspicuous part in this.

CHRONIC INFLAMMATION. INTESTINAL TUBERCULOSIS. This is seldom a reason for surgical intervention in the case of the small intestine. It presents two types, the ulcerative and the hyperplastic or fibrous.

Ulcerative Tuberculous Enteritis. This is comparatively common in patients with



Foreign-body tubercle in wall of colon in segmental or regional colitis. If such a tubercle develops less completely it may be solid and be mistaken for a tuberculous lesion.

pulmonary tuberculosis, or it may be caused in children by infection through milk carrying the bovine type of bacilli. Archibald, cited by Boyd, finds that it usually starts in and about the cecum and spreads along the ileum and ascending colon alike. The ulcers originate in the lymphoid tissue of the Peyer's patches and solitary follicles and spread out from these in a circumferential direction, while typhoid ulcers remain limited to the lymphoid tissue and their long axes lie in that of the bowel. Tuberculous ulcers here are like those anywhere, but it is well to emphasize that they tend to cicatrize the wall of the intestines with consequent deformity and obstruction. They very occasionally perforate and require surgical intervention to close the defects thus caused and head off generalized peritonitis. One may recognize these ulcers from the appearance of the serosa beneath them, which usually shows a seeding out of small, glis-

tening tubercles in the lymphatics, often like chains of tiny beads

Hyperplastic Fibrous Tuberculosis This differs from the form just described in that it is accompanied by a marked fibrous overgrowth of the connective tissue which produces a thickened, rigid segment of bowel much like that noted in regional enteritis, but minus the acute superficial inflammatory features. There are numerous ill defined tubercles and groups of giant cells scattered throughout the mucosa as well as the wall, but no caseation of note. The disease usually affects young adults, begins in the cecum about the ileocecal valve, and spreads up the ileum and colon simultaneously.

BOECK'S SARCOID OF THE INTESTINES In this disease any part of the intestines may be invaded, and one will find the typical fibrous tubercles scattered in the submucosa and muscular wall. Grossly, the diagnosis is very difficult and it is only after one finds the characteristic Boeck's tubercles, with their giant cells possibly containing "asteroid bodies," that one realizes that this is not true tuberculosis. (See Boeck's Sarcoid, p. 154.)

Tumors The intestinal tumors will be considered as a group at the end of the section on the colon, as they are more or less common to the entire length of the intestinal tract.

APPENDIX

This little vestigial organ provides the bulk of surgical pathologic material in most general hospitals on account of its well known propensity to become inflamed and, having done so, to cause a variety of complications. Appendices removed at operation should always be examined and usually reported upon as this may constitute documentation for future statistical study or prove of value in case of lawsuits.

The organ is situated at the lower end of the cecum and springs from its lower and inner aspect, usually it is directed inward and upward, but it may be recurved and

come to lie behind the cecum, where it becomes embedded in inflammatory adhesions if it becomes infected. It may then present a problem in surgical technique before it can be extricated and removed from its lair. Sometimes, particularly if it is very long, it hangs over the pelvic brim into the pelvis. If the entire cecum is very mobile or (owing to faulty embryonic development) is not situated in its usual position, it may carry the appendix to portions of the peritoneal cavity where one would not expect it to lie. Fairly frequently it may be found in the right upper quadrant. Its usual length is about 7 cm., it may vary from 4 to 12 cm. without being particularly abnormal. Its usual diameter approaches 5 to 7 mm., but it may vary a few millimeters either way. It bears no proportion in its size to the age or sex of the individual, as it may be enormous in children and pitifully small in large adults. It is pinkish brown in color, usually soft and flexible, but if its muscle is contracted it may be quite cylindrical, straight and rigid.

Microscopically its mucosa resembles that of the large intestine in a general way, but it contains much more lymphoid tissue in the form of follicles that are closely set, and it has two muscular coats—an inner circular and an outer longitudinal layer. The muscularis mucosae is comparatively insignificant, and between it and the muscular wall there is a fibrous capsule of loose connective tissue sometimes called the "capsule of the submucosa", in the case of obese subjects this may contain a good deal of adipose tissue. In the muscular wall is found a variably prominent nervous apparatus composed of ganglia and nonmedullated nerves, this is the myenteric plexus of Auerbach. A similar but less conspicuous plexus lies just beneath the submucosa or in its outer portions and is known as "Meissner's plexus."

The mucosa is composed of glandular crypts comprising goblet cells and argentaffin cells of Kulshitzky, together with a few of the fuchsinophil granular Paneth

cells, which are not as numerous here as in the rest of the lining of the alimentary tract. The lymphoid tissue is abundant in children up to the age of about 16, when it should begin to undergo appreciable diminution or atrophy. The appendix of a normal adult exhibits lymphoid follicles that are spaced along the submucosa and form a single layer; in children they may be in several strata and appear to jostle one another, so closely are they set.

The organ has been described here in its normal state for the specific reason that it is so important in surgical pathology that one must have solid criteria for judging aberrations from the normal.

Anomalies. The appendix may be lacking entirely, and very rarely a double organ has been observed.

Trauma and Vascular Disturbances. These are of comparatively little importance; much used to be written anent foreign bodies, but most of these proved to be fecaliths, which are inspissated and more or less calcified particles of feces. One occasionally finds toothbrush bristles, bits of glass, or other small objects like pieces of hair or bone in the organ.

The appendix may be traumatized by worms, the chief offender being the pinworm, or *Enterobius vermicularis* (older name: *Oxyuris vermicularis*). One may find from two or three to forty or more of these in the appendix of a child, very rarely in that of an adult. The females are larger and flatter than the males and resemble small nail-parings in their appearance and rigidity. They are about 4 mm. in length and about 1 mm. at their middle. The males are often missed, as they are shorter and more slender. They leave pinpoint erosions in the mucosa which may bleed slightly. Whipworms (*Trichuris trichiura*) are very occasionally met with. These are much larger than the enterobii and have long, thread-like cephalic extremities and a stouter body with a rounded caudal extremity. The importance of these worms lies in the fact that they produce the typical

symptoms of an acute attack of appendicitis, and usually their presence in the appendix is quite unsuspected until they are found there after it has been excised. The connection between verminous infestation and the symptoms of appendicitis is very obscure; we must content ourselves for the present with the statement that it exists.

Inflammation. Appendicitis is a disease of civilized people; unless they take to eating the food of these, primitive and "uncivilized" individuals rarely suffer from it. Boyd cites Lucas-Championnière, who found one case in 22,000 patients among Romanian peasants, while in the cities of Romania the incidence was one in 22. The disease is very rare among the so-called "savage" tribes.

There appear to be two exciting causes of appendicitis: obstruction and infection. The main routes of infection are two: hematogenous (more common in winter, when respiratory infections abound) and mucosal (more usual in summer, when gastro-intestinal infections are most frequent). As to obstruction, this most usually follows the impaction of a fecalith which effectually plugs the organ and converts it into a closed sac. Appendices with fulminating inflammation below such an obstruction and a comparatively normal mucosa and wall proximal to it are observed so often that one cannot fail to take this into serious account. The organ may be obstructed by kinking caused by adhesions in its vicinity, or by masses of worms, or by the swelling of the mucosa in chronic lymphoid appendicitis. Spasm of the sphincter, which Boyd notes as resisting a pressure of 40 mm. of water, is also to be considered as a factor. Such obstruction interferes with the circulation (may even cut it off entirely, in fact), and there is dilatation of the lumen distal to it with an accumulation of material that affords an excellent culture medium for organisms which cannot possibly be evacuated into the cecum. The excellence of the medium may depend upon the presence of proteins, as the disease is far more prevalent

among meat eating people than among vegetarians. It is rare in the very young and the very old and commonest in young adult males.

ACUTE CATARRHAL APPENDICITIS In most instances this is a "textbook disease," and too much stress should not be laid upon it from the practical point of view, as it

wall is little affected. The condition goes over into the next to be described.

ACUTE SUPPURATIVE APPENDICITIS This is the commonest appendiceal lesion. It varies from a mild extension of the picture just described to a complete disruption of the organ by a gangrenous process. At first the appendix is swollen, and its vessels are



Cross sections of pinworms (*Enterobius vermicularis*) in lumen of vermiform appendix. Sharp spines at either side of periphery of sectioned worms represent lateral flanges or ridges cut transversely. Bladder like vesicles just within thick chitinous wall of worm are muscles.

seldom appears among the laboratory specimens. The reason for this is that it constitutes the earliest and mildest form of infection and inflammation of the appendix, affecting chiefly the mucosa and lamina propria and not invading its wall. The appendix is swollen and slightly reddened, while its mucosa is swollen and may be fairly red and covered with an excessive amount of mucus.

Microscopically, it is noted that the goblet cells of the mucosa are engorged with mucus, the submucosa is hyperemic and edematous, and its census of plasma cells and eosinophils is increased, with a few polymorphonuclear neutrophils present. The

injected like bright red threads upon a pinkish serosa that is at the outset shining, but becomes dull and gradually coated with shreds and then sheets of fibrin like wet tissue paper. Next it becomes a bright cherry red, its walls thick and firm, and its mucosa swollen and flushed, then granular and eroded by small ulcerations. Purulent exudate may accumulate in its lumen and cause "empyema" of the appendix, or small abscesses may develop in the wall. As the process continues, the wall becomes necrotic, the muscle loses its tone and is flabby, and the appendix may become as variegated in color as an ecchymosis, running the gamut from bright red to yellow.

ish green, grayish green, dark red, and finally almost black. The fibrin may be replaced by a fibrinopurulent exudate, with pus showing on the surface.

At this point in the process several things may happen: the pressure within the lumen may force a "blowout" or perforation, with discharge of the contents into the peritoneal cavity; if this does not take place suddenly, the appendix can be surrounded by omentum and the perforation can take place into its embracing mass of fat, where it forms a localized "appendiceal abscess." Thus sudden perforation means general peritonitis, gradual perforation a localized abscess. Often the surgeon will believe that perforation has taken place when the pathologist cannot find an actual opening in the wall; this merely indicates that a portion of the wall is pervious to bacterial penetration and that the organisms have made their exit without there being any actual fistula through which feces or pus might escape. Further complications depend upon the pattern taken by the inflammation. After general peritonitis numerous focal abscesses may be left among coils of intestines that adhere to one another, and these (or the type of appendiceal abscess just described) may infect the portal circulation and bring about pylephlebitis (inflammation of the portal vein) or the thrombosis of mesenteric vessels. Copious hemorrhage seldom takes place after perforation, as the appendiceal vessels are well closed off by the inflammation. An appendiceal abscess can occasionally cure itself by working its way toward the pubic rim and over Poupart's ligament to the groin, where it points up through the skin, appearing as an inguinal abscess.

If an acute attack is not interfered with there is always a chance that the process will regress and the organ return almost to normal, as would any other inflamed part under favorable circumstances. With this in view many physicians used to "wait out" an attack, which was a great mistake, as the outcome of the disease is quite unpredictable. The subsidence of an acute attack of

suppurative appendicitis will usually be followed by the formation of scars in the wall of the organ and by organization of the fibrinous exudate over its surface, which results in adhesions. Scars and adhesions predispose to obstruction, and thus a vicious circle is set up.

Acute suppurative appendicitis may be subdivided into two groups: acute diffuse and acute focal suppurative appendicitis, terms that need little elaboration. The focal type of inflammation is very apt to occur when a fecalith is impacted not far from the tip of the organ, or a kink develops in that situation; then the organ is inflamed not diffusely, but rather focally. The tip of the organ may be the seat of intense suppurative inflammation while the rest of the appendix is fairly normal in appearance.

SUBACUTE APPENDICITIS. There are two types of this: it may begin and continue as a subacute inflammation, or it may represent a recurrence of an acute one. The former is occasionally seen and its gross



Midwall of appendix in subacute appendicitis, usually called "chronic." Note scarring, fatty invasion of submucosal capsule, and diffuse cellular exudate. This is the result of a succession of attacks of acute diffuse suppurative appendicitis, usually mild in nature.

pathology is not very different from that of a mild acute appendicitis. Under the microscope, however, the picture differs in



Very low powered view of a transverse and a longitudinal section of appendix in acute diffuse suppurative appendicitis. Note marked disruption of the architecture, destruction of mucosa, and infiltration of wall by polymorphonuclear leukocytes.

that there is an exudate which is rich in eosinophils, plasma cells, and lymphocytes, rather than consisting of neutrophil polymorphonuclears. The condition is of more academic than practical interest.

In the second type, generally known as "chronic appendicitis," one observes a rather fibrous organ that is not acutely inflamed, but exhibits a varying amount of fibrous adhesions. The wall may be slightly thickened. Microscopically one finds small ulcers in the mucosa that are shallow and superficial, irregular areas of scarring in the wall, relatively prominent and overgrown myenteric plexuses that may show fibrosis, and possibly an increase of fat in the fibrous capsule of the submucosa. Mason has laid great stress upon the proliferation of "neuromuscular bundles" that appear to grow out from the nerve plexuses into the submucosa until they may form considerable masses or neuromas.

Such appendices, if left to themselves, usually do one of two things: either they continue to "grumble" and ultimately become fibrotic, with their lumen obliterated

by fibrous, nervous, and lymphoid tissue, or they succumb to an acute suppurative attack or "flare up." Patients with such organs usually give a history of repeated bouts of right lower quadrant pain, nausea, vomiting, and fever; these clear up in a few days to be repeated in a relatively short space of time. The patient usually shows leukocytosis and may present focal rigidity and spasm.

CHRONIC LYMPHOID APPENDICITIS. This is quite different in its pathology from the subacute variety. It follows prolonged inflammation of the lymphoid elements of the appendix, falling into the category of chronic lymphoid inflammations such as are presented by the tonsils and by the mesenteric and other lymph nodes under certain conditions, in fact it often coexists with chronic enlargement of the mesenteric lymph nodes.

The conception just set forth is one that was advanced by Letulle and has been taken up by various Italian investigators, among them Beluffi, who summarized the clinico-pathologic picture in 1936. Fausset collected

over 100 cases in our hospital in 1939, correlated the clinical and pathologic findings, and came to a complete accord with Beluffi's conclusions.

The disease is characterized by a slightly swollen and pale appendix that shows a vigorous protrusion of the mucosa and sub-



Detailed view of lymphoid apparatus of appendix in chronic lymphoid appendicitis. Overgrowing follicles are crowding out mucosa and usurping space of submucosa. Muscularis is not shown.

mucosa when transected and a lumen that is well-nigh closed by the swelling and corrugations of the pale mucosa. Under the microscope three stages may be recognized: (1) an early hyperplasia of the lymph follicles which gives way to (2) an atrophy of this tissue with the formation of a continuous cylinder about the lumen quite devoid of clear-cut follicles ("sclerotic atrophic stage" of Beluffi), and this, in the end, is succeeded by (3) the stage of fibrosis and obliteration of the lumen with the disappearance of most of the lymphoid tissue and all of the mucosa. In the first stage the epithelium of the mucosa is attenuated over the lymphoid tissue and may present as a single layer without any crypts. In the final

stage this disappears and the site of the lumen is marked by a central strand of mixed connective and lymphoid tissue with an admixture of nervous elements. It will be noted that the process centers in changes in the lymphoid elements: first they are so hyperplastic that they may form several layers of large follicles, then they fuse to form a single layer of lymphoid tissue. For this reason the term "lymphoid appendicitis" seems appropriate.

Patients with this disease have repeated bouts of cramps and pain in the right lower quadrant; they usually have nausea, and about half of them give histories of vomiting during an attack. Spasm and rebound tenderness are usually lacking, although there may be slight rigidity on palpation. These digressions into clinical description are helpful and aid the pathologist, as well as pointing to a distinct difference in the general reactions to the two types of "chronic appendicitis." It should be noted that severe acute suppurative appendicitis, long-standing subacute appendicitis, and chronic lymphoid appendicitis may all wind up in the same terminal condition of fibrosis and obliteration of the lumen, with the organ resembling a bone knitting needle in its appearance. Some anatomists maintain that senile involution may produce the same picture, but they seldom if ever possess clinical data on the cadaver, so that this assumption should be accepted only with considerable reserve.

MUCOCELE. An appendix that has been acutely inflamed, and in which proximal occlusion takes place through cicatrization, becomes completely sealed off and turns into a simple pouch. Mucus is secreted into this pouch in the usual or increased amounts, and since it cannot escape, the organ becomes distended with it and the secretion becomes inspissated and gelatinoid. It may then force its way through the wall and dissect channels along the subserosa, not only of the appendix, but of the cecum as well. There it may form large accumulations of gelatinoid matter under

PLATE III



The appendix (*Top*) Normal appendix showing the slight injection of its vessels incidental to removal

(*Middle*) An acutely inflamed organ (acute diffuse suppurative appendicitis) Note its redness and the patches of fibrin over and near tip

(*Bottom*) A gangrenous appendix with a perforation near tip A fecolith was impacted at junction of distal third with proximal two thirds of the organ

the serosa (pseudomyxoma peritonei) A frequent cause of this is the actual severance of the appendix from the cecum by a distal gangrene and perforation After the abscess that forms has been drained, the proximal end of the thus isolated appendix heals over, effectively closing the lumen and forming a sausage shaped sac filled with



Topographic photomicrograph of transverse and longitudinal section of appendix in chronic lymphoid appendicitis. Note disproportionate thickness of lymphoid layer

mucus This may become infected anew and occasion a fresh attack of suppurative appendicitis Rupture of such a mucocoele will result in the spilling of its contents into the peritoneal cavity and the production of numerous deposits of mucus that resemble the pseudomyxomas noted in connection with ruptured pseudomucinous adenomas of the ovary Although these mucocoeles of the appendix are usually not very large (the average being about 8 cm in length and 1.5 cm in diameter), some of them have been reported as "enormous"

ACTINOMYCOSIS Appendicitis due to actinomycotic infection runs a rather subacute course, the patient is not much prostrated and the surgeon is astonished to find a large, swollen organ that is apparently acutely inflamed On section the wall is found to be very much thickened and fibrotic, and the lumen may contain yellowish "sulfur granules" that suggest carcinoid if they are buried in the mucosa, these are colonies of the ray fungus Microscopically there is a

picture of rather lively subacute inflammation, and the pathologist is likely to overlook the fungi unless he searches for them carefully or happens to stumble upon a colony

Although the pathologic picture is very characteristic, aside from the colon of actinomycetes, the subsequent events are most typical After apparently healing, the appendix quite unexpectedly develops a fistula which may open into the operative wound or burrow down into the pelvis to communicate with the bowel or, in women, with the vagina Thus a noisome tract of infected granulation tissue is created, and such fistulae are very difficult to eradicate A fatal outcome after a slow and prolonged illness is not uncommon The disease is usually secondary to actinomycosis of the cecum, which explains the recurrence after the formation of fistulae by a respread of the infection

TUBERCULOSIS One might expect this to be rather common, but only one instance among thousands of appendices examined in the course of hospital routine shows evidence of the disease It may, however, be secondary to cecal tuberculosis or to tuberculous salpingitis, occasionally it is apparently primary in the appendix, which is little changed in appearance It seems to be large and pale appearing at most unusually moist and unhealthy Under the microscope one observes scattered tubercles of the specific variety that usually show caseation in some of them, these may be situated in the mucosa or in the wall of the organ

Tumors The tumors of the appendix should be considered here, rather than in the section dealing with tumors of the intestines in general, because of peculiarities inherent in new growths of this small organ The appendix presents the same possibilities as other portions of the alimentary tract for the formation of tumors, but only a few of these possibilities ever produce tumors and of those that do produce them only one is a prominent histologic unit in the col-



Section from appendiceal carcinoid impregnated with silver by Laidlaw method. Note tiny black granules in cytoplasm of typical argentaffin cells (Army Medical Museum 61609, acc no 42333).

position of the appendix. The epithelium, which is so prolific in the production of tumors elsewhere in the alimentary tract, gives rise to no polyps of consequence, and carcinoma is so rare that few pathologists have ever seen one that would stand the test of critical diagnosis. The so-common carcinoma of the cecum may surround the ostium of the appendix completely, but it appears never to transgress its portals—a fact for which the sphincter may in some way be accountable. Of the thousands of appendices examined in the New York Hospital during the past twelve years, not one showed true carcinoma; two examples of carcinoma, however, were submitted in consultation from other hospitals.

CARCINOID. This is a growth which, when it arises in the appendix, is almost invariably noncancerous. Usually it is discovered at operation for some other condition, or at necropsy, without having caused any symptoms of note. The appendices bearing such tumors are usually short and stubby with a bulbous, clubbed extremity that may measure over 1 cm. in diameter. When this bulb is transected, a poorly defined lumen is noted, together with a thick wall filled on one side with yellowish masses of tumor that are fairly hard. Under the microscope there are seen islands of polygonal cells scattered throughout the organ in a rather haphazard fashion; some of them are in the submucosa, some invading the muscularis. These are chromaffin cells which are likewise argentaffin with a granular cytoplasm in which the granules become yellowed with chromium salts and blackened by those of silver; in the latter case they may appear as microscopic black rings. The nuclei of the cells are delicate and almost exactly spherical, nucleoli are not prominent, the cytoplasm is granular, and the cellular outline polygonal or cuboidal. Usually the complexes of cells are solid, but they may form suggestions of acini or tubules, in which case the tumor takes on a more glandular appearance.

Because of the argyrophilia, Masson has

attributed these cells to the proliferation of Kulschitzky cells of the mucosa which have the same trait; he believes that these become dedifferentiated and then proliferate and wander into the submucosa and thence to the muscularis. His theory has been generally accepted, although it is admittedly difficult to confirm his observations in all carcinoids, some of which show no detectable connection with the mucosa after careful examination in serial sections. It is possible that paraganglionic cells in the plexuses of Meissner and Auerbach have something to do with the origin of the tumor. Elsewhere we shall consider these tumors in their malignant form; for some obscure reason they are frequently malignant when they arise in the small intestine, metastasizing widely but slowly and killing by equally slow stages. Why this tumor should be noncancerous in the appendix and cancerous when it occurs practically next door to it has yet to be explained; the neoplasm is exactly the same in its appearance in both situations.

LYMPHOID TUMORS. Very occasionally tumors are encountered that, in the gross, suggest carcinoid because of the production of a bulbous appendiceal tip and the presence of yellowish tissue about the lumen and in the wall. On microscopic examination, however, these prove to be lymphoid; sometimes they are immature and sarcomatous, sometimes they show few if any mitotic figures and give the impression of being true lymphomas. In either instance, unless they are accompanied by similar changes in neighboring mesenteric nodes they are not clinically malignant, as their removal ends the matter and they do not recur at the site of the appendicectomy. They may attain a diameter of 1.5 cm. or slightly more.

NEUROGENOUS TUMORS. Masson has described an "appendiceal neuroma"—a tumor composed of coiled neural sheaths and trunks that grows in the site of the obliterated lumen of fibrous appendices. It may be questioned whether or not this is a true

linear cracks or defects in the anal mucosa, possibly showing some fibrin and acute inflammation in their depths and being surrounded by a zone of subacute inflammation

Hemorrhage from hemorrhoids is common and may be sufficiently copious as to cause marked anemia. That hemorrhoids may be the starting point of carcinoma in the rectum and anus cannot be denied, as they are constantly irritated and inflamed, it is remarkable, though, that carcinoma so seldom develops out of the thousands of varicosities.

Inflammation The acute inflammations, other than regional colitis (which is essentially similar to regional enteritis), are of little importance as surgical problems. There may be volvuli, mesocolic thromboses, and the like, which can cause massive necrosis and necessitate removal of portions of the colon.

ULCERATIVE COLITIS This disease (of obscure etiology but usually attributable to organisms of the dysentery group of bacilli) causes extensive ulceration of the mucosa, the ulcers being of irregular outline, size, and shape and often confluent, so that geographic areas of denudation appear on the surface. They are covered with grayish sloughs and the mucosa near them is swollen and edematous, often becoming redundant and polypoid. Their edges are not particularly thickened nor undermined, they seem rather to be more or less punched out and shallow. This is confirmed by the microscope. The wall about the lesion exhibits inflammation of a subacute type, sometimes containing very acute foci if there has been a recent exacerbation of the condition. In its late stages the lesion is recognized, on examination with the x ray, by "pipestem" shadows which represent a much narrowed and straightened lumen without its normal haustrations. In any stage the sigmoidoscope will reveal the shallow ulcers. The rectum may become involved and provide another reason for rectal biopsies.

AMEBIC COLITIS AND PROCTITIS In this the protozoan *Endameba histolytica* is the causative agent, the bowel is the site of numerous ulcers that are deep and undermined and communicate by means of submucosal necrotic tracts. The entire mucosa becomes a complicated worm burrow. The margins of the ulcers are reddened and thick, somewhat like those of malignant ulcers. Microscopically one finds a corresponding picture of subacute inflammation, loss of superficial mucosa, and the deep pits in which the amebas lie. With the proper technic, which usually presupposes the use of iron hematoxylin in some form, these can readily be recognized and differentiated from the resident cells like the monocytes, which are so often mistaken for amebas by inexperienced observers.

When examining suspected material one should never give a positive diagnosis of amebiasis if the cells show large, ovoid nuclei, the nucleus of the ameba is disproportionately small for the size of the cell, it is perfectly spherical, and its chromatin and membrane stain like delicately etched dots and lines. It is about the size of a monocyte and it ingests erythrocytes, but there the similarity stops. The chromatin of the nucleus of the ameba is grouped into radially arranged clumps just within the nuclear membrane like the counterbalances of a balance wheel in a watch, the nucleolus is small and inconspicuous, unlike that of some of the rarer amebas which may present prominent "bird's eye" nucleoli. In searching for amebas in sections it is best to look for their burrows in the mucosa and not to waste time on the surface of the mucosa or the depths of the intestinal wall.

LYMPHOGRANULOMA VENEREUM This disease produces atypical lesions in the rectum and its walls. The typical granulomas are described in the chapter on lymph nodes, they differ entirely from the rectal granulomas in their histologic appearance. The rectal lesion is a chronic, cicatricizing one characterized by the presence of large numbers of plasma cells, with little else to mark

tumor; tumors are composed of cells, not cellular processes, and these have all the appearance of the so-called "amputation neuromas" which follow injury and irritation. There is no doubt that this proliferation of nervous elements may be seen under these circumstances, but although Mason and his collaborators report it as common among the French and the French Canadians, only one or two good examples have come to our notice in New York Hospital.

LARGE INTESTINE

The colon, including the cecum and the rectum, suffers from many of the ailments of the small intestine, but presents some that are peculiarly its own. Among inflammations, tuberculosis, regional enteritis, and a few such conditions are common to both of these segments of the intestinal tract; tumors in the colon are not very different from those in the small intestine.

The large intestine differs anatomically from the latter inasmuch as it has three externally located taeniae, or tape-like muscular bands that pucker its wall into innumerable bulging pockets or "haustrations," which may lead off into diverticula under fairly normal conditions. Furthermore, its histology is somewhat simpler and its physiologic function is more one of absorption than of secretion and digestion. It constitutes the dehydrating segment of the intestinal tract, absorbing much water from the fecal contents and moulding them into the familiar form. It fairly teems with resident micro-organisms, some of which (like the colon bacillus) may readily become pathogenic under proper conditions, and it may harbor several species of pathogenic protozoa (*Endameba histolytica* among them).

Congenital Anomalies. Most of these have to do with atresias in the rectum and anus which result from faulty development of these from the cloaca. They may be solid and several centimeters in length, or they may take the form of thin diaphragms across the lumen. There may be failure of

development of a longitudinal septum between the rectum and the urogenital system, with rectovesical, rectovaginal, and other such fistulae resulting. Considerable variations may be noted in the length of the mesocolon and the development of the attachment of the ascending colon, so that this may be fairly movable or fairly fixed, as the case may be. The cecum may come to lie almost under the margin of the liver as a result of faulty rotation during embryonic development.

Vascular Disturbances. HEMORRHOIDS are so prevalent that they make up a steady supply of usually uninteresting material for the pathologic laboratory. Essentially they are varicose veins (see chapter on Cardiovascular System), those of the hemorrhoidal plexus of the rectum being affected. They may be roughly divided into the internal and external varieties—a distinction without much pathologic but with considerable surgical difference. The former are found above, the latter at or below the anal sphincter.

Hemorrhoids are caused by anything that promotes varicosities: pregnancy, constipation, prolonged exertion, pelvic tumors, and other similar obstructive phenomena. Subjected to constant trauma from hard fecal material in a warm and moist region, they are apt to become inflamed and may be infected as well. Thrombosis is usual, the vein becoming plugged by a thrombus, experiencing more or less acute inflammation, and causing much pain and discomfort. The hemorrhoid then undergoes organization and fibrosis, and fibrous tabs are produced; this is so common in the perianal region that few people escape having one or two such tabs in later life. They are a constant source of annoyance, as they interfere with cleanliness and are apt to be associated with fissures that develop in their neighborhood. These are shallow cracks in the mucosa that always give rise to marked pruritus if not to sharp lancinating pains that are out of all proportion to the insignificant size of the lesion. The fissures are not interesting under the microscope, as they are merely

linear cracks or defects in the anal mucosa, possibly showing some fibrin and acute inflammation in their depths and being surrounded by a zone of subacute inflammation

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its nature. As few stenosing lesions of the rectum are rich in these cells it is well to inquire into the history of the case; usually one will elicit the information that the patient is a woman, or a male with abnormal sexual habits. In women the propinquity of the vagina and the rectum affords a ready opportunity for rectal infection, either along

colon are of unknown etiology; possibly they represent small points of weakness in the wall, possibly the outpocketings are more or less natural. As they develop in elderly people, they may represent a part of senescence and senile degeneration. When they are very numerous the condition is known as diverticulosis. They are small,



Submucous lesion of tuberculosis in transverse colon. Tuberculous tissue is interrupting glandular architecture at one point. In this way an ulcer may originate.

the perineum or through the rectovaginal septum. Without a Frei test a positive diagnosis of this disease on a biopsy from the rectum must be subject to revision.

INFECTIOUS GRANULOMA. Tuberculosis may not uncommonly affect the large as well as the small intestine and take on similar forms. The diffuse fibrous variety is readily mistaken for regional colitis and vice versa. Syphilitic colitis is distinctly rare; illustrations of an instance of this lesion as described by Foucar are shown on the following page. Not only was the lesion gummatous in this instance, but treponemata were demonstrable as well.

DIVERTICULITIS. The innumerable small diverticula that develop in the course of the

tubular outpouchings of the mucosa through the muscular wall, about 4 or 5 mm. in length. Usually they are near the points of entry of groups of vessels, and thus they are similar to the Rokitansky-Aschoff sinuses to be described in connection with the gallbladder. They may become infected and inflamed and give rise to acute symptoms reminiscent of those of appendicitis, particularly if the diverticulum is situated in the ascending colon. The fact that some of them possess a very narrow opening into the bowel makes it natural for them to retain fecal material, thus facilitating infection. The inflammation may spread to the surrounding adipose tissue of the appendix epiploica, in which

PLATE IV



(*Top*) Acute Meckel's diverticulitis with early gangrene. The diverticulum projects like a thumb from segment of ileum which is also involved in the inflammation, necessitating resection of 12 cm. of viscus. End to end anastomosis of ileum was followed by complete recovery.

(*Bottom*) Annular carcinoma of transverse colon. Note double frill or lip, with trough of ulceration between overgrowing marginal mucosa, and disparity of the circumferences of the segments of gut. That proximal to the lesion is dilated on account of obstruction.



the diverticulum lies, and a "peridiverticulitis" may develop. Perforation of diverticula and resulting local abscess or peritonitis is said to be a common occurrence, although it has not been so in our experience. It is an ever present possibility, however.

IRRADIATION COLITIS This is not a true inflammation, but it borders upon chronic inflammation inasmuch as it produces enormous amounts of cicatricial fibrous tissue



Oil immersion photomicrograph of field in gumma of transverse colon shown below. Levaditi impregnation demonstrates many trypomastix. Patient had been inadequately treated with anti-luetic. (Army Medical Museum 64153)

and resulting stenosis and stricture. A loop of sigmoid overlying the uterus, for example, may have been repeatedly transirradiated during a course of therapeutic exposure of a more deep seated carcinoma of the uterus or ovary. After a time—sometimes months or years—the tumor may have disappeared through surgical intervention or irradiation, but the patient gradually begins to suffer from obstruction of the lower bowel. When the offending loop is surgically removed it will be found to have been converted into a fibrous pipe with a point of maximum stenosis and a dilated lumen proximal and a constricted or collapsed lumen distal to the obstruction. Signs of inflammation will be limited, under microscopic examination, to the marked fibrosis that occurs and a moderate lymphocytic infiltration. As the lesion is late in developing and intensive irradiation is only beginning to come under critical retrospect, it is likely that this lesion may be quite frequently encountered during the next few years. Two such instances have thus far come under the present writer's observation.

Hirschsprung's Disease (Megacolon)

This is an infrequent lesion that is char-

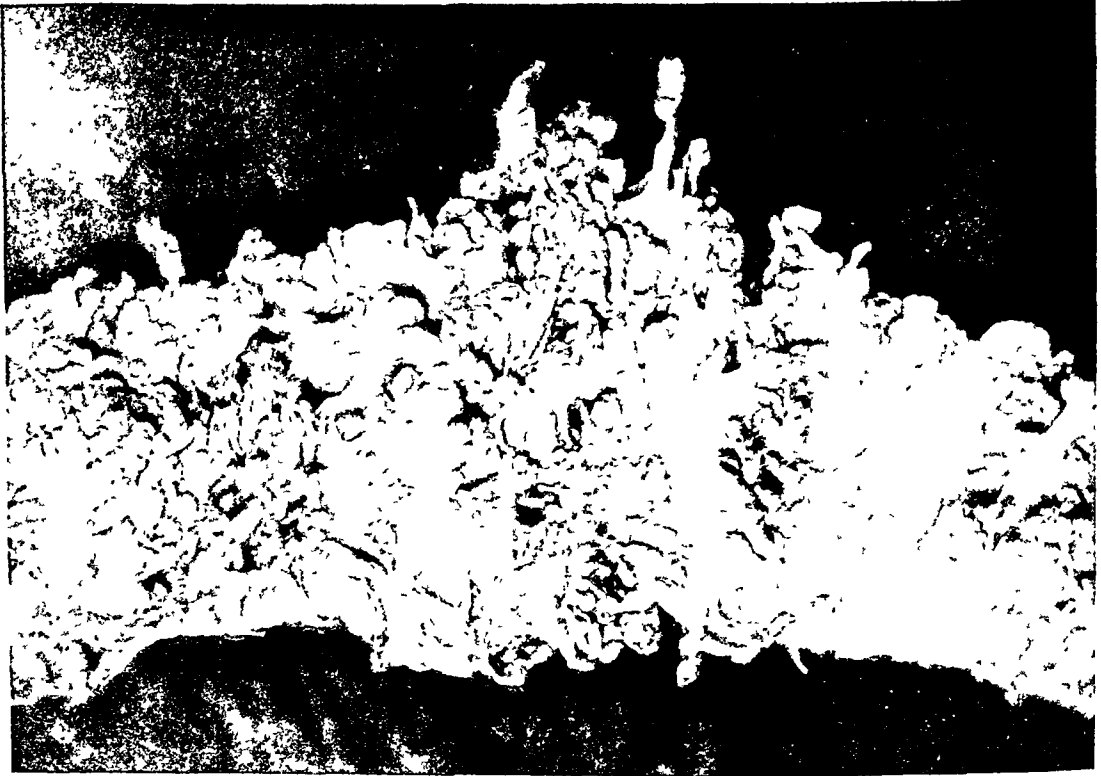


Low powered photomicrograph to demonstrate area of gummatous thickening in wall of transverse colon (Col F H Foucar)

acterized by enormous enlargement and bloating of the entire colon. It is progressive and usually fatal, and it occurs in children—boys more often than girls. The disease is unaccompanied by any very characteristic symptoms, but the clinical signs are helpful: gradual enlargement of the abdomen associated with obstipation and

tion to the colon through chronic inflammation of the colon and obstructions from adhesions. Possibly this constitutes a form of senile atony with relaxation of the wall through loss of normal tonus.

Tumors of Intestinal Tract. **EPITHELIAL GROWTHS. "POLYPS."** The simplest and most frequently seen tumor of the intestine is



Pronounced polyposis of transverse colon. The plumper polyps are of adenomatous type; the more slender are examples of ordinary or "polypoid" type. (Col. F. H. Foucar.)

a massive evacuation of feces and gas following spinal anesthesia. Naturally, a barium enema will make the condition evident on x-ray examination. Its cause is obscure, but most authorities consider it to be a dilatation and hypertrophy due to constriction at the sigmoidorectal junction caused either by spasm or by kinking in consequence of an abnormally long sigmoid. Boyd mentions its improvement after a left-sided splanchnicotomy as a proof that it is due to spasm in the region just mentioned. Pathologically there is little to be remarked, as the condition of the gut is one of dilatation plus hypertrophy.

There is a type of secondary megacolon that occurs in the elderly following obstruc-

tion to the colon through chronic inflammation of the colon and obstructions from adhesions. Possibly this constitutes a form of senile atony with relaxation of the wall through loss of normal tonus.

the so-called "polyp," which is small, spheroidal, and almost membranously thin, and is mounted at the apex of a triangular stalk with an approximate altitude of a centimeter or so. The mucosa over this pedicle is thin and normal, while that which forms the ball-like head of the polyp is overgrowing and redundant, with well or partially differentiated cells, imperfect goblet cavities, and either more or less mucus than normal. Apparently these balls of adenomatoid hyperplasia become involved in the peristaltic waves of the bowel and are tugged upon until the submucosa beneath them is drawn out into the thin triangular pedicle just described. They may become 5 cm. in length.

Such polyps may be found anywhere in the intestines, but most frequently they are situated in the transverse and descending colons. They may arise singly, in small numbers, or by the hundreds, in which case the resulting condition is known as "polyposis." The polyps are fragile and readily damaged; they may become twisted and slough away spontaneously, and, of course, they frequently bleed copiously. Their most dangerous feature is the possibility that they may become malignant. In polyposis one can never predict which polyp will undergo such a change; repeated biopsies through the sigmoidoscope may eventually produce an example of carcinomatous change. The average polyp measures about 5 to 7 mm in the diameter of its "head." Polyps are conveniently removed by fulguration or snaring, but when they are present in vast numbers a radical operation is often preferable to a long period of expectant treatment until a carcinoma develops.

ADENOMA Intestinal adenomas are merely exaggerated polyps which usually lack the polyps' long pedicle, usually having instead a small, short one or occasionally none at all, being sessile. They are berry shaped and slightly acuminate, and they may have a papillary surface composed of fine papillae that give them a somewhat cauliflower-like appearance. They are firm and apt to be quite brilliantly red, and, like the polyps, they may become spontaneously detached, appearing then in the patient's stools. Although usually they are not much over 1 cm in diameter, they may attain considerable size; intestinal adenomas 10 cm in length and 4 cm in diameter have been noted, but this is exceptional.

Microscopically the adenomas exhibit the same sort of overgrowing mucosa noted in the polyps, usually very actively secreting mucus. There may be considerable metaplasia, and when this is noted together with mitotic figures the appearance of the tumor is indistinguishable from that of cancer. In such a case the question arises as to the

advisability of radical operation, unless there is definite invasion of the pedicle. Such tumors may be removed by local fulguration or snare and treated as though non-cancerous; they will not recur and there is no reason for considering them anything but academically malignant (Ewing has called this type of adenoma "adenoma malignum"). If such a tumor should be definitely sessile, however, and without any



Field from "adenoma malignum" of rectum, showing slight metaplasia at lower left. If pedicle has not been invaded these may be safely removed with a snare or by fulguration and may be forgotten. When sessile, they are to be regarded as true carcinomas.

discoverable pedicle, it should be considered as cancerous and a radical removal of the tumor-bearing segment of intestine should be recommended.

In cases of intestinal polyposis it is not at all uncommon to find polyps in large numbers, a smaller number of adenomas, and one or two frankly cancerous growths in addition; for this reason these cases always present diagnostic, therapeutic, and operative problems. Colectomy is usually the last resort, but probably the inevitable one, so that it should always be seriously considered in connection with multiple polyps of long standing; an early radical operation may prevent a later carcinoma. Irradiation is not of any use in these cases.

CARCINOMA Carcinoma of the intestines is far more commonly seen in the large

bowel than in the small one, where it is relatively rare. A peculiarity of carcinoma of the colon is the fact that it often attacks young adults, men and women in their twenties sometimes being affected and people of 35 to 45 frequently so. This is not to say that elderly subjects are not affected by this type of carcinoma; on the contrary, most of the patients with these tumors are elderly. Another peculiarity of this group of carcinomas is that they metastasize late in the course of their growth, so that prompt recognition of their presence and their removal usually effects a cure. They spread first to the regional lymph nodes in the mesocolon or the perirectal tissue, where the metastases may be removed with the tumor; "telemetastasis," or metastasis to distant parts, occurs late in the course of the tumor, in contradistinction to that which characterizes so many other carcinomas. Changes in bowel habits, bleeding from the rectum at stool, and marked loss of weight should arouse suspicion of their presence; early and thorough sigmoidoscopy may reveal the tumor when it is still young and small. Many of the patients operated upon at our hospital have had these tumors without their being diagnosed until they were discovered through digital and proctoscopic examinations as part of the ward routine. The patients, coming to the hospital for some completely different reason, may have casually mentioned changes in bowel habit and "piles" in the course of giving a clinical history. This, therefore, is a plea for routine rectal examinations on all patients seen for the first time, if there is the slightest indication of rectal abnormality in the history.

Carcinoma of Small Intestine. In the small intestine, where carcinoma is infrequently noted, it usually takes the form of a button-like lesion that may begin as an adenoma, or it may develop from the mucosa. In either instance, it tends to spread circumferentially around the bowel wall, where it produces a marked fibrosis of desmoplastic reaction and a lesion that has

been aptly likened to a napkin ring. This gradually closes down the lumen as it grows, finally shutting it off so completely as to cause obstruction or obstipation. Naturally, such a lesion may ulcerate and usually does so, with consequent mixed infection; the added feature of edema may assist materially in effecting blockage of the lumen. A great many of these lesions seem to consist of two rings with a wide, deep groove between them; this is because there is a circumferential ulcer with two raised, everted lips that constitute respectively the proximal and distal rings, while the bed of the ulcer forms the groove. Microscopically, the tumors are adenocarcinomas that are not particularly specific in their appearance. There may be profuse mucus secreted, with the production of a mucous carcinoma. The growth almost invariably spreads through the entire muscular wall and infiltrates the muscle above and below the obstruction.

Carcinoma of Large Intestine. Carcinoma is most often found in the sigmoid and rectum; next in frequency come the cecum and ascending colon; following this the two flexures and the transverse colon. The tumors are grossly very much alike, and too great an adherence to classification is inadvisable. They may begin in sessile adenomas, then developing into bulky, fungating masses with the appearance of cauliflower; they may arise as buttons that are slightly undercut around their margins and go on to ulceration, spreading up and down as well as around the wall of the intestine if this is roomy like the cecum and ascending colon, or growing in a circumferential fashion and causing napkin-ring lesions if the bowel is of a lesser caliber, as in the upper ascending colon, the flexures, and the lower sigmoid. In the rectum they show a great variety of gross forms which probably have little distinguishing significance. The important features are those that invite obstruction and bleeding and betray the presence of the lesion early in its development.



Area of carcinomatous metaplasia intercalated between rectal glands near an adenocarcinoma of rectum. Such areas indicate multicentric origin.

ADENOCARCINOMA There are three general microscopic varieties of adenocarcinoma that have some prognostic significance.

1 *The usual form*, which is similar to the adenoma malignum, comprising large acini and crypts lined by lawless cylindrical epithelium that shows no goblets.

2 *A multiacinar form*, characterized by numerous connected acinar structures composed of cuboidal or low columnar cells, which invades the mucosa in a number of places at once or may have multicentric origin in the mucosa. These are usually more invasive and more malignant than those described in the preceding paragraph.

3 *A small celled type*, showing solid alveoli resembling those of the carcinoid and evidencing considerable invasive tendency and a very definitely malignant nature. Stout has attempted to connect such a type with an origin in the cells of Ersbamer, who recognized three stages in the development of his "basigranular cells": an argyrophil, one that could take up silver but not reduce it, and a third that was even more primitive. Such tumors should, then, occasionally show argyrophilia, the few that we have observed have not as a rule

done so, but one of them was almost entirely composed of argyrophil cells.

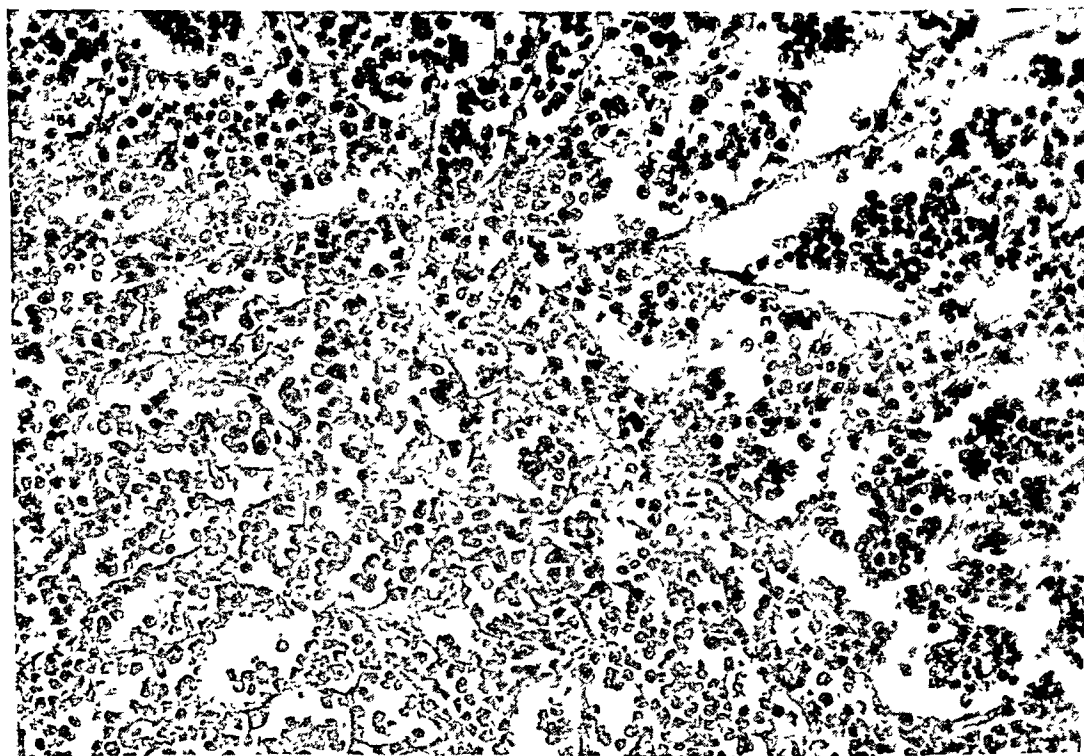
EPIDERMOID CARCINOMA Hypothetically, this tumor may develop anywhere in the intestinal canal by a process of metaplasia of its glandular elements, actually, however, it does not seem to do so. Rather, it is limited to the anal region where, as is the case with carcinoma of the esophagus, it may invade the rectum by transgressing the limiting pectineal line at the junction of



Typical adenocarcinoma of rectum undermining normal mucosa.



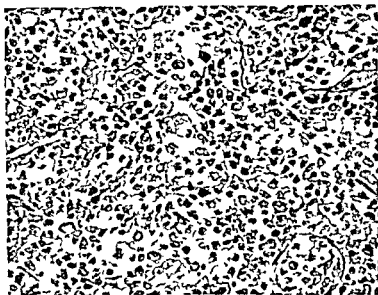
Multiacinar and more malignant type of carcinoma of colon invading musculature of wall of that viscus.



Small-celled carcinoma of rectum—an unusual form, possibly allied to carcinoids of that organ. While it resembles lymphosarcoma superficially, its architecture is similar to that of adenocarcinoma.

the glandular epithelium of the rectum and the epidermoid epithelium of the anus. This it does by massive overgrowth or by the infiltration of small masses of tumor just beneath the mucosa. It is difficult to distinguish these tumors with the naked eye with any assurance, except that they manifestly involve the perianal skin and are hence presumably epidermoid. Under the microscope that exhibit the same appear

ever, as Oberndorfer first showed, they may develop distinctly malignant characteristics when they arise in the jejunum or ileum, and they then cause slight local destruction which in and of itself is neither extensive nor important, but which may herald widespread metastases to other parts of the body, especially the liver, which is reached through the portal system of lymphatic and hemal drainage. The tumors do not grow



Rectal carcinoid impregnated with silver. Small black cells are completely filled with argyrophil granules.

ance as that of any epidermoid or "squamous celled" carcinoma. They are very malignant, and they tend to recur and to metastasize to the inguinal lymph nodes. In this they differ from the more slowly metastasizing glandular carcinomas of the bowel proper.

CARCINOID. This has been considered already under the section on the appendix; it remains merely to remark that it may occur anywhere in the intestinal tract and rarely in the stomach. In the small intestine necropsy will occasionally reveal inconspicuous little yellow tumors which prove to be carcinoids on microscopic examination. They are then to be considered as constituting early and as yet innocent forms which probably correspond closely with those of the appendix. Occasionally, how-

as rapidly as the metastases of carcinoma, and they kill the patient by slow and often painless stages, chiefly through the toxemia and profound cachexia that they occasion. Being argentaffin and neurogenous, they are resistant to x rays.

MUSCULAR TUMORS OF INTESTINES. LEIOMYOMA. Leiomyoma of the intestine is not at all rare; it develops within the muscular coats and produces a growth that may be small and spherical or that may attain considerable size. It is light brown, well circumscribed, and rubbery; its importance lies in the fact that it may cause obstruction, because the mucosa that covers it may become ulcerated and bleed, or because the tumor may be caught in a peristaltic wave and occasion intussusception. Micro-

scopically it does not differ from leiomyomas in other organs.

LEIOMYOSARCOMA. Rather occasionally one encounters malignant tumors of smooth muscle that are outwardly very much like the innocent leiomyomas; their difference lies in the malignant and primitive histologic appearance of their cells and their rather slowly progressive malignant clinical course. They are in no way different from those we have considered in the case of the stomach.

LYMPHOSARCOMA OF ALIMENTARY TRACT. This tumor may occur in any segment of the alimentary tract. In the 20 cases collected by McSwain and Beal from the records of the Department of Surgery in the New York Hospital, the following distribution was noted: esophagus, 1; stomach, 7; small intestine, 3; appendix, 2; large intestine, 7. Three of the last seven were in the rectum. All these cases were observed within the span of nine years.

Lymphosarcoma is seldom diagnosed before operation. It may be suspected at operation if there is extensive involvement of the lymph nodes in the vicinity of the tumor. The gross appearance of the growth is not distinctive, but one may often be struck by the fact that it is apparently intramural and covered by a relatively natural mucosa. Microscopic examination reveals the typical characteristics of lymphosarcoma. This may be one of any of the types described under that heading in the pathology of the lymphoid apparatus. The tumors are usually infiltrative; when they are fairly well circumscribed, as may be the case, they present a more hopeful prognosis, as they may be entirely extirpated.

Although lymphosarcoma has a bad reputation in the literature, our experience was more favorable than might have been expected: nine of the twenty patients are alive without recurrence. Some of these have passed the five-year mark. Roentgen therapy gave the usual immediate good results, although one or two patients were unable

to continue with it on account of violent reactions. It was found, however, that the best results were obtained in the cases of those patients in whom the growth was localized and hence completely removable by operation. It is also true that the prognosis depends upon the type of the tumor: the lymphocytic (small-celled) lymphosarcoma affords the best outlook for a cure, while the lymphoblastic is accompanied by a poor prognosis.

NEUROGENOUS TUMORS. These are very rare but may occur in the intestines, appearing as neurofibromas and neurilemmomas or as malignant varieties of these, the neurogenous sarcomas. They are apt to be hard and nodular; on section they are succulent and moist and resemble edematous fat, but they are so much firmer than adipose tissue that one is not apt to make any mistake concerning them. (See Tumors of Nervous System.)

MELANOMA. The melanomas are neurogenous tumors, and as such they will be discussed in the chapter on the nervous system. As they arise in distorted tactile corpuscles of the skin, the so-called "Hassall's bodies," they could not be expected to occur in the intestinal tract except in the one situation where they are occasionally found (usually in their malignant form) the anal canal, which is lined with epidermis and develops from the ectoderm. They therefore occupy the region of the pectinate line and may be mistaken for unusually brown, thrombosed hemorrhoids. Under the microscope they reveal the "sarcomatous" type of melanoma—one composed of large, irregular, fusiform cells that contain much melanin and correspond to those that constitute the "blue moles" of the skin, tumors that are subcutaneous. Like malignant melanomas anywhere they are metastatic and very dangerous. They should be widely extirpated.

VASCULAR TUMORS. The usual varieties of vascular tumors may be found in the alimentary tract, but not at all commonly.

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Typical condyloma acuminatum from perianal region. Most of cellular overgrowth is limited to rete malpighii

with the connective tissues. Their importance in the intestines lies in their obstructive tendencies and the fact that they may excite intussusception.

CONDYLOMA ACUMINATUM. A common growth about the anus is the condyloma acuminatum, also found about the external genitalia. It is questionably a tumor and represents a local, papillary overgrowth of epithelium in which the individual papillae are bulbous or pointed ("acuminate") and covered by a thick layer of epidermis in which the chief proliferation centers in the malpighian layer. There is no invasion of the underlying tissue and no metaplasia. If the warts are removed with a cautery, they will not recur, if they are merely cut off, however, they will not only recur but will tend to seed themselves out over a still wider area of perianal skin. They strongly suggest a viral origin which is yet to be proved.

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14

Liver, Gallbladder, and Pancreas

LIVER

ATROPHY, DEGENERATION, AND NECROSIS
INFLAMMATION
CIRRHOSIS
INFECTIOUS GRANULOMA
PARASITES
TUMORS

GALLBLADDER

CONGENITAL ANOMALIES
PHYSIOLOGIC CONSIDERATIONS
HISTOLOGY
METABOLIC DISTURBANCES

GALLBLADDER (*Continued*)

INFLAMMATION (CHOLECYSTITIS)
TUMORS
BILIARY DUCTS
HISTOLOGY
TUMORS
PANCREAS
VASCULAR CHANGES
INFLAMMATION (PANCREATITIS)
CYSTS
TUMORS

LIVER

This, the largest organ in the body, impinges only incidentally upon surgical pathology on account of the fact that it has thus far been impossible to extirpate the liver, hence surgical procedures are usually confined to the incision and drainage of abscesses, the removal of parasitic cysts, and similar conservative operations (The gallbladder and biliary ducts are quite another story, constituting a very important field of surgicopathologic endeavor) Nevertheless, the surgeon frequently takes biopsies, particularly bits of hepatic tumors, upon which the surgical pathologist must pass judgment

The congenital anomalies of the liver itself are not of a type that lend themselves to surgical procedures

Atrophy, Degeneration, and Necrosis Brown atrophy and also pressure atrophy of the liver may be dismissed with mention, as may the small focal necroses of acute infectious diseases Small areas of peripheral necrosis with bile stasis may be noted in connection with obstruction of the common duct and should be recognized when observed

ACUTE YELLOW ATROPHY This condition has a rather broad range of etiologic factors it may occur in pregnancy, it may follow acute infectious diseases like typhoid, or it may be caused by a variety of chemicals, particularly the fat solvent anesthetics like chloroform, some of the anthelmintics such as carbon tetrachloride or bisulfide, and toxic preparations like phenylcinchoninic acid or its salts (cinchophen, atophan, tolysin, etc), which affect susceptible subjects often enough to make them dangerous in physiologic dosage The organ is the seat of massive necrosis that reduces it in size until it may become half its original dimensions, it is flabby and its margins become attenuated and sharp, in acute cases its color is a brilliant yellow, while in subacute ones there is an admixture of red, which is partly due to hemorrhage and partly the result of regeneration of hepatic tissue The process (if the patient survives it) results usually in a great deal of fibrotic scarring, although sometimes healing may be remarkably complete and fibrosis not marked The microscope reveals extensive central necrosis of the hepatic lobules, areas of hemorrhage, and marked fatty infiltration of the

parenchyma (which may be simulated by hydropic degeneration, particularly in the case of poisoning by phosphorus). About the periphery of the lobules and in the neighborhood of the ducts one may find regeneration going on *pari passu* with the destructive process.

ACUTE CATARRHAL JAUNDICE. As this is seldom fatal, we know relatively little about its pathologic features, but the epidemic jaundice of the military forces has been studied by Lucké and others in very recent investigations, and, as the patients may be killed in the course of bombing attacks or by other such accidental causes in hospital camps, necropsies have been performed upon them in all stages of the malady. Apparently the disease has much in common with acute yellow atrophy, but differs in its almost invariable tendency to heal completely and leave no trace of the lesions that were present at the height of the attack of jaundice. It causes no fibrous scars.

AMYLOIDOSIS. Occasionally a surgeon will take a biopsy of an amyloid liver, which is large, waxy, and reddish brown, and under the microscope the pathologist will find deposits of amyloid which may be metachromatically stained rose red with gentian violet or deep mahogany brown with iodine in alcoholic solution or as IKI. Amyloid also takes on Congo red very intensely. It is best to employ frozen sections, for although positive stains may be obtained on a temporary basis in material embedded in paraffin, they fade in a few hours and are lost. The amyloid is found to lie along the walls of the sinusoids, where it occupies the space between the capillary walls and the hepatic cords. It resembles the waxy casts of the kidney and gives the impression of having been injected from a tube into the spaces it occupies. It is almost invariably the result of wasting diseases, prolonged suppuration, or cancerous tumors. Its chemistry is still a matter of considerable uncertainty.

PIGMENTATION. The liver may be the site of hemosiderosis, with deposits of hemo-

siderin in the Kupffer cells; or of hemosiderin, in which not only iron-containing hemosiderin, but a lipid pigment known as "lipofuscin" or "hemofuscin" may also be found. Anything obstructing the outflow of bile from the organ will bring about an obstructive jaundice in which bile is backed up into the capillaries, where it collects in the form of tiny plugs and gives the organ a brownish to deep olive-green color, depending upon the length of time the obstruction has been present. Common-duct stones and carcinoma of the region of the papilla of Vater (in the common duct, the duodenum, or the head of the pancreas) are probably the commonest causes of such stasis.

Inflammation. ABSCESES. The important forms of inflammation of the liver, from the surgical viewpoint, are those that lead to the production of abscesses. One may observe large solitary abscesses which may be incised and drained, or multiple small examples which present no such simple solution. Abscess of the liver, as seen in our latitudes, is usually secondary to an infection in the peritoneal cavity that reaches the organ through the portal system (suppurative pylephlebitis), or to pyogenic infections in the neighboring thorax, with subdiaphragmatic abscess that invades the liver from above. All in all, however, the *Endameba histolytica* is probably responsible for more abscesses the world over than any other causative agent.

Abscesses present ragged cavities of necrotic material in the substance of the organ, with walls that show little fibrous reaction. Amebic abscesses are particularly untidy and "worm-eaten" in their appearance; they tend to be solitary and to spread slowly in the face of fibrosis. Of the microscopical findings there is little to be said, except that a careful search should always be made for amebas, which are present more frequently than one would suppose. Emetine therapy reduces their numbers and renders demonstration very difficult.

Occasionally endemic outbursts of amebic

dysentery may follow the infection of a large number of persons through the ingestion of food prepared by a carrier of amebas in their encysted form, as was the case in the well remembered Chicago endemic of a few years ago. The amebas have the same characteristics in the abscesses that they show in the colonic lesions, but usually they are much harder to find on account of the welter of pus and necrotic hepatic tissue in the abscess cavity.

Cirrhosis As this condition brings about extensive liver damage and for that reason interferes with the function of that organ, biopsies are sometimes carried out in the course of laparotomies to determine the type of the lesion. These biopsies are small and may be poorly chosen, usually being taken from the sharp margin of the organ, which at this time may be converted almost entirely into connective tissue. The somewhat varied forms of hepatic sclerosis constitute the nucleus of a great deal of discussion and classification, they have very little to do with surgery, and yet some curious surgeon is always removing "a little snip of liver" in the hope that something pertinent to his diagnosis will turn up, therefore it behooves the pathologist to be familiar with these cirrhoses.

LAENNEC'S CIRRHOSIS This is the "alcoholic cirrhosis" of many textbooks, the "atrophic cirrhosis" of others. In it the hepatic lobules become involved in a fibrous overgrowth that is variously interpreted as constituting fibrous increase or (as Mallory used to claim) disappearance of parenchyma with condensation of the surviving stroma which gives the appearance of fibrous increase. Both factors probably should be taken into account. This cirrhosis is regularly associated with ascites and may often show varying degrees of jaundice. Various toxic materials appear to be the causative agents, although experiments and experience in the clinic may differ widely. For instance, alcohol in spirituous liquors appears to influence the production of cirrhosis, but alcohol per se will not produce it in experi-

mental animals. Mallory felt that copper and other heavy metals were at fault and that in cheap liquor such metals could be traced to faulty distillation and contamination by metallic parts of the stills. The experimental agents that have been successfully used run the gamut from simple chemicals such as magnesium chlorid and colloidal silica to coal tars and Witte's pep tone.

At first the liver shows a good deal of fatty infiltration and resembles that of habitual beer drinkers, but it soon becomes fibrotic, and the end stage of the process is the "hobnail liver" with dense connective tissue outlining small nodules of a few millimeters' diameter that represent atrophic parenchyma. Microscopically one may confirm the strictly perlobular distribution of the increased fibrous tissue, and one will find a lively proliferation of small bile ducts that sometimes produce almost adenomatous pictures in the portal triads, where portal vein, hepatic artery, and biliary duct are grouped. Naturally, a liver that is as fibrotic as this compresses the hepatic and portal circulations and obstructs them, so that advanced cases of cirrhosis exhibit the "caput medusae" of distended superficial abdominal veins about the umbilical region. These attempt to provide a collateral circulation that will by-pass the obstruction. Ascites used to be ascribed to the same cause, but is now believed to be the result of disturbed metabolism with increased globulin in the albumen globulin ratio of the blood plasma.

OBSTRUCTIVE BILIARY CIRRHOSIS (CHARCOT'S CIRRHOSIS) This may simulate the preceding type, but it has its origin in an ascending chronic inflammation of the biliary tree due to obstruction and stagnation. Microscopically there is evidence of this chronic inflammation in the triads, with generalized lymphocytic infiltration there and along the walls of the sinusoids.

CAPSULAR PSEUDOCIRRHOSIS As surgeons usually take their biopsies from the sharp margin of the liver where they can get

tissue with a minimal amount of hemorrhage, this superficial pseudocirrhosis affords a stumbling block that is difficult to surmount. It has the appearance of atrophic cirrhosis, but is found to extend only a few millimeters or a centimeter or so beneath the capsule; a positive Wassermann reaction is of value in making a differential diagnosis. There is little difficulty in demonstrating the superficial nature of the lesion, but with a living patient this is not so readily accomplished. A history of multiple serositis, a chronic infection, or other data may be of value.

HYPERTROPHIC BILIARY CIRRHOSIS (HANOT'S CIRRHOSIS). This type is mentioned in every textbook, but it is seldom seen as Hanot described it. Probably most instances of this lesion are due to lues. It has always loomed large in French and French-Canadian literature, but it seems to be very rare indeed outside of French purloins. Certainly in this country it is most often met with in cities where there is a high incidence of luetic complications. The disease may occur in children. It enlarges the liver and is characterized by an intra- rather than a perilobular cirrhosis which breaks up the hepatic lobules into small groups of cells surrounded by collagenous fibers. This lends to the organ a finely granular appearance on gross inspection, and it is confirmed by microscopic examination of sections. Jaundice is associated with the lesions.

Rezek has described a type of intralobular cirrhosis that he observed in India which appeared to be caused by the eating of hot spices; it usually appeared in boys, rather than in girls, who were denied the choice condiments bestowed upon their brothers, particularly upon the oldest brother. Rezek then experimented with animals to which he fed these spices, producing identical lesions in their livers.

Infectious Granuloma. HEPATIC SYPHILIS. The liver which is typical of this disease is known as the "hepar lobatum" on account of the coarse distribution of the sclerosis and the consequent formation of

coarse and irregular lobules by rather widely separated scars. Gummas of the liver are not uncommon and may be mistaken for tumors and removed by operation; they present the typical appearance of the tertiary syphilitic lesion and are usually accompanied by conspicuous formation of scars throughout the organ and the production of syphilitic cirrhosis.

TUBERCULOSIS. This is common in miliary tuberculosis, but it does not constitute a surgical entity; multiple conglomerate tubercles of the liver may simulate carcinoma very closely and be mistaken for multiple metastases. The tubercles in this form of the disease are from 1 cm. to 2 cm. in diameter and roughly spherical; they may even present a deceptive umbilication of their sectioned surface. Microscopically they are readily recognized as tubercles.

Parasites. ECHINOCOCCAL CYSTS. The liver is frequently the site of echinococcal cysts, the larval forms of a short tapeworm, the *Taenia echinococcus* that infests the intestines of dogs. For this reason the disease is commonest among people who live in close association with dogs, shepherds of Central and Northern Europe and Australia being often affected. The embryos hatch from eggs that are ingested by the host and find their way from the alimentary tract to various organs; the liver, being situated on the "portal line" of circulatory drainage, is the first and most usual organ to be affected. Here the larvae become encysted and multiply by a budding out of daughter larvae from the inner surface of the wall of the "mother cyst" so that several generations are produced in one cyst. The liver may be riddled with them, or there may be only one or two which may attain formidable proportions and measure 15 cm. or more in diameter. Such a cyst has a fibrous membrane composed of the host's connective tissue, inside of which there is a laminated chitinous lining that is milky white and resembles the "skin" of a hen's egg in some ways. Within this lining membrane, which is produced by the larvae, is a gelatinous

PLATE V



The gallbladder (*Top*) A chronically inflamed gall bladder with an acute inflammatory episode. Its fundus shows a diverticular "Phrygian cap," or unfused terminal vesicle. This is a congenital anomaly that is fairly commonly observed.

(*Center*) An acutely inflamed organ with several faceted composite stones. Note the deep, murex red color and the thick, brawny wall.

(*Bottom*) A typically "strawberry" gallbladder (cholesterosis) with a single cholesterol stone.

tissue with a minimal amount of hemorrhage, this superficial pseudocirrhosis affords a stumbling block that is difficult to surmount. It has the appearance of atrophic cirrhosis, but is found to extend only a few millimeters or a centimeter or so beneath the capsule; a positive Wassermann reaction is of value in making a differential diagnosis. There is little difficulty in demonstrating the superficial nature of the lesion, but with a living patient this is not so readily accomplished. A history of multiple serositis, a chronic infection, or other data may be of value.

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material in which are embedded the daughter cysts, each a few millimeters in diameter

Before resorting to surgery in suspected cases, one may perform serologic tests with aspirated fluid, which will act as an antigen and produce a precipitin when mixed with the patient's blood serum. Examination of

common. They inhabit the bile ducts or portal vessels and bring about chronic inflammation and obstruction. *Ascaris lumbricoides* may blunder into the common duct and cause symptoms of stones there, together with obstruction and jaundice. In a personally observed instance a patient



A bit of the wall of an echinococcus cyst. It is composed of chitin, and floating in fluid of cyst, are two immature echinococci. One is cut in longitudinal section (left) and represents an entire scolex.

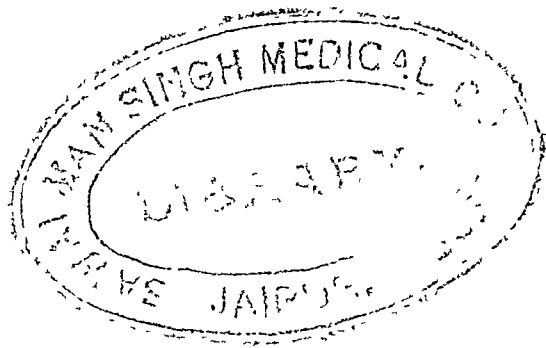
the fluid under the microscope after sedimentation often reveals typical hooklets, representing the teeth that have been set free by the decomposition of the larvae. The hooklets are chitinous and resist decomposition, so they may survive the larvae a long time. Naturally, the liver is destroyed by the presence of the cysts.

OTHER PARASITES There are a number of flukes or platyhelminths that may invade the liver, particularly in the Orient, where human excreta are used as manure. Such worms include the *Opisthorchis felinus*, *Clonorchis sinensis*, *Schistosoma mansoni*, *Fasciolopsis buski* and others that are less

common. They inhabit the bile ducts or portal vessels and bring about chronic inflammation and obstruction. *Ascaris lumbricoides* may blunder into the common duct and cause symptoms of stones there, together with obstruction and jaundice. In a personally observed instance a patient

was cured of all symptoms when she vomited an ascaris after this had been accidentally expressed from the common duct into the duodenum during an operation for suspected impacted calculus of the duct.

Tumors The liver is a very common site for tumors, as it lies in the portal circulation and metastases from neoplasms drained by that circulation are readily conveyed to the hepatic sinusoids, where they lodge and set up tumors. The liver is then peppered with yellowish white metastatic nodules which show a typically umbilicated sectioned surface, are firm and well delimited, and are a frequent source of surgical biop-





Primary hepatic carcinoma apparently arising in neighborhood of junction of hepatic cords and bile ducts. Note vague resemblance to hepatic tissue.



Tubular carcinoma primary in intrahepatic bile capillaries of the liver of an elderly woman. In younger patients the growth is less orderly and much more rapid, showing more mitotic figures.

sies. Sometimes the tumors are typical enough for the surgical pathologist to make a definite diagnosis and predict the primary site with accuracy, but very often the tumors of the alimentary tract are so similar to one another that he is limited to making a simple statement that it is a metastasis from an unknown primary site.

HEMANGIOMA. Cavernous hemangioma of the liver is fairly common; it probably represents a hamartoma or developmental defect in the complicated vascular system of the organ. It may attain a diameter of 15 to 20 cm. Hemangioma usually arises near the anterior margin of the left lobe and presents insoluble problems in surgery, as it is so rich in blood that operation is apt to terminate in fatal hemorrhage. Irradiation may cause it to shrink by bringing about extensive thrombosis and organization of the thrombi. Malignant tumors, or angiosarcomas, are not particularly common in this situation. They may be multiple and more or less invasive, with ultimate metastasis.

ADENOMA. Hepatic adenomas or simple "hepatomas" are uncommon; they may be single or multiple, and they represent an overgrowth of hepatic tissue which, under the microscope, might be said to resemble "scrambled liver." The cells form foci of distorted hepatic architecture that reminds one of that seen in adenomas of the suprarenal or kidney: they are well differentiated but poorly arranged. These tumors secrete bile in some instances; as the liver shows differentiation into hepatic cords and biliary ducts these adenomas may resemble one or the other of these elements.

MESODERMAL HEPATOMA. L'Esperance has described a number of tumors arising in the connective tissue of the liver, and the present writer has seen one case in which the liver was thickly strewn with small tumors resembling metastatic nodules or tubercles which, on microscopic examination, proved to be composed of cells resembling those of reticular tissue and producing an abundant reticulum. Such tumors may develop malig-

nant varieties with a slight tendency to local metastasis.

CONNECTIVE-TISSUE TUMORS. As there is much connective tissue in the liver, fibromas are a possibility, but they are of rare occurrence and one seldom encounters them. Sarcomas of the liver, which occur with almost equal rarity, may be of the fibroblastic, reticular, or endothelial variety (the last-named being derived from the vascular endothelium).

CARCINOMA. Primary carcinoma is noted more often in males than in females, and there is usually an antecedent history of some degree of cirrhosis as a predisposing factor. It may occur in young adults without any antecedent cirrhosis. In young patients its course is very rapidly fatal, being reckoned in weeks. It takes two forms and, like the adenoma, may arise from hepatic cords or from biliary ducts, from each of which typical carcinomas may develop; those from biliary ducts are by far the commoner.

Primary Parenchymatous Carcinoma. This tumor may attain diameters of from 8 to 10 cm. It is firm, fades off into the surrounding parenchyma, and is usually definitely bile-stained, although that feature may be absent. Microscopically it is seen to be composed of distorted hepatic cells which, according to the type of the tumor, may show fair differentiation or be very irregular in size and shape and produce neoplastic giant cells of a very bizarre appearance. With a little care the pathologist can usually demonstrate masses of bile pigment within the cells, and this is taken to be an important indication that the growth is primary and of parenchymatous origin, as the cells of the ducts would not secrete an appreciable amount of bile. The neoplasm metastasizes within the liver itself and to other organs by way of the circulation.

Biliary-duct Carcinoma. The more usual form of primary hepatic carcinoma, sometimes known as "carcinoma adenosum," is generally white, granular, and very firm

ever, one finds that it contains only a small proportion of the day's total output of bile—too little to be of any particular use as a reserve supply. This led early investigators to conclude that it was a vestigial organ like the appendix, with no function. Further observation, however, proved that it is distinctly an absorptive organ, and the work of Rous and McMaster, which demonstrated this, stimulated other investigators. Boyd found that a solution of ferric anide of potash could be injected into the gallbladder and followed through the lymphatics, draining the organ. This led some to believe that the gallbladder is a "one way or dead end street," absorbing bile and its products without discharging these into the duodenum. This belief was held in face of the fact that the organ is provided with a stout musculature which, in the case of biliary obstruction, becomes definitely hypertrophied.

The "one way" idea was exploded by the observations of Boyden, Whittaker, and others who remarked that the reason that the organ was not seen to contract during operations depended upon the anesthetic, which paralyzed it. Under local anesthesia the organ did contract under certain circumstances, which were later proved to be the stimuli presented by fatty food in the duodenum. In experimental animals a dose of egg yolk would cause a fairly prompt evacuation of the contents of the gallbladder a short time after its administration. Still later it was discovered that an injection of secretin would do the same thing, indicating that a hormone is produced in the duodenum in response to the presence of fatty material and thus brings about the reaction. Much work was accomplished by means of the injection of lipiodol, or the exhibition of halogen compounds of phenolphthalein (tetra iodophenolphthalein), which visualized the organ and thus enabled one to follow its expansion and contraction in vivo under experimental conditions in the human subject.

Finally, the nervous control of the organ

and of the biliary tree was worked out, and it was established that the vagus controls contraction of the gallbladder and expansion of the common duct and antrum of the ampulla, while the sympathetic system causes relaxation of the muscle and contraction of the sphincter of the ampulla. This would be a simple formula were it not for the fact that there seems to be an added factor of elastic recoil that is occasioned by the flow of bile into, rather than from, the organ, which sets up a rhythm.

Apparently, then, the gallbladder serves as a means of concentrating bile by absorbing its water and of increasing its viscosity by adding to it mucus from its glands without diluting it, dilution is a function of the glands of the cystic and common ducts. Thus a rather mysterious organ has been shown to be a delicate and purposeful adjunct to the liver. The fact that a great deal of this experimental investigation was carried on in the '20's accounts for much of the misunderstanding that still lingers in the minds of older physicians. The physiology of the gallbladder is excellently discussed by Whipple in Nelson's *Looseleaf System of Surgery*.*

HISTOLOGY

The histology of the gallbladder is of considerable importance in interpreting its pathologic changes. It has a mucosal lining which, under a binocular dissecting microscope, appears not unlike a rough stucco in its architecture, structures which resemble villi in microscopic sections prove to be cross sections of ridges that tend to enclose quadrangular spaces, like a miniature arrangement similar to that of the valves of Heister in the neck of the organ, but much smaller. Heister's valves are like a series of uncapped boxes that are best seen in dried specimens. The mucosa of the gallbladder overlies its muscularis almost immediately; there is no submucosa or muscularis mucosae, as there is in the appendix, and

*New York: Thomas Nelson & Sons.

It may attain even larger size than the parenchymatous type. Microscopic sections reveal a composition consisting of distorted biliary ducts with a resulting and decidedly tubular architecture. It is invasive and may metastasize within and outside of the liver. Both forms of hepatic carcinoma present inoperable conditions, and irradiation with the x-ray is all that can offer any hope of curative treatment; it is none too successful, at that.

SECONDARY HEPATIC TUMORS. The malignant melanoma may convert the liver into a veritable plum pudding studded with brown to black tumors varying from a few millimeters to a centimeter or two in diameter. These are very variable as to pigmentation, however, and one sometimes sees generalized metastases that exhibit pigmented tumors in one organ, while those in another (the spleen, for instance) are quite colorless. One should always be on the lookout for nonpigmented metastases of these melanomas, which may be diagnosed from carcinomas by a careful study of their architecture and by the use of silver impregnations which will "silver" nonpigmented granules of premelanin (which is colorless) almost as well as they will granules of melanin that is brown before treatment.

The liver is a "way station" on the line of metastases from the abdominal cavity through the portal system to the lungs and general circulation, hence it presents a catch basin in the form of innumerable sinusoids in which neoplastic cells may lodge, and one may find metastases from carcinomas of the intestinal tract or stomach, from the ovaries and testes, from renal tumors, and so on. It is also possible for metastases to reach the liver in the reverse direction from the lungs; bronchiogenic carcinomas are frequent offenders in this respect.

GALLBLADDER

This organ is probably second to the appendix as regards its appearance on the table of the surgical pathologic laboratory; usually it arrives there as a result of in-

flammation rather than because it is the site of new growth, which is relatively uncommon in this situation.

Congenital Anomalies. As the gallbladder is an outgrowth of buds from the midgut there may be disturbances in the development of these which will interfere with that of the gallbladder itself, or of the cystic, common, or other ducts. This leads to congenital atresias of the bile ducts that are discovered a week or so after birth through the presence of jaundice, lack of bile in the stools (acholia), and faulty digestion of fats.

The gallbladder is formed by the fusion of a "terminal vesicle" and the fundus. The terminal vesicle is a spherical structure which in the process of development should fuse completely with the gallbladder to constitute its distal extremity, leaving behind no vestige of this fusion. Occasionally, however, there is a trace of this separation in the form of a circular ridge at the line of fusion, the vesicle forming a pouch like a liberty cap at the tip of the organ. This is very evident in "visualized" gallbladders in x-ray films and is known by the roentgenologists as a "Phrygian cap." Pathologists have often mistaken this terminal pouch for a diverticulum, as stones are often found impacted in it.

The gallbladder may be partly covered with peritoneum and partly attached to the liver, which is its normal state; or it may be elongated and "free floating," being almost entirely enclosed in peritoneum; again it may be almost entirely embedded in the substance of the liver, with only its fundus protruding through a fenestrum in the hepatic margin.

PHYSIOLOGIC CONSIDERATIONS

Before the gallbladder's pathology is discussed it might be well to outline briefly some of its physiologic features. Naturally, a small bladder growing as an offshoot of the biliary tree would at first be interpreted as a sort of expansion chamber or a storage space for bile. As one investigates it, how-

but the best examples of cholesterosis are seen in conjunction with subacute cholecystitis in which the mucosa becomes reddened and, when cholesterol deposits streak and dot its surface, sufficiently resembles that of a strawberry to be called a "strawberry gallbladder."

Gallstones Much can be written concerning these, probably too much has already been said. They are the result of two processes—disturbed equilibrium in the biliary constituents (cholesterol and pigment) and inflammation that causes desquamation of epithelium and exudation of pus, both of which may form protein nuclei for "compound" stones. In the first instance one sees either single stones of pure cholesterol that may resemble masses of camphor or multiple small stones (exactly like yellow mulberries in their appearance) that may measure up to a centimeter in diameter. If the biliary pigments are precipitated the resulting stones will resemble cinders, or even flat, scaley clinkers of a jet black color. In the second instance, the compound stones are not made up of pure radiating crystals but are composed of laminae of alternating cholesterol, pigments, and possibly admixtures of lime salts about a central protein nucleus, the source of which has already been explained. These compound stones represent the results of inflammation.

Compound stones may be ovoid, spherical, cylindrical, or faceted in a variety of ways. The faceting is supposed to be the outcome of intertrition, or mutual grinding. Some pyramidal faceted stones, however, suggest that (as Sweet has assumed) they have been cast or molded in the boxlike Heister's valves, into which (after the specimen has been dried) these stones may be fitted with great accuracy. They show little evidence of attrition, and they may be graded into groups of different sizes without any intermediate forms. One of these groups will be found to fit certain valvular recesses, another certain others, and so on. Thus there is considerable evidence that they are molded, not ground. There is also

plenty of evidence, however, that other stones have been ground off on one or another surface—particularly the large spherical or ovoid varieties that may show concave facets. The stones vary in size, shape, color, and consistence according to their chemical composition, those containing calcium carbonate or phosphate and those that are chiefly pigment are very hard, while those that are largely composed of cholesterol (and they constitute the majority of all gallstones) are soft and friable. Their color varies from white, in the case of the calcific forms, to jet black. Occasionally they may be perfect replicas of a child's jackstones, with the same projecting bars with rounded tips that distinguish these toys. Sometimes a stone will form a cast of the entire lumen or cavity of the gallbladder and will measure 10 x 4 x 4 cm in size. Almost as often the organ will be filled with hundreds of small stones like kernels of yellow corn that pack its lumen to the exclusion of most of its bile. Stones that originate in the common duct are reddish brown and very soft and putty like, differing radically in their appearance from those that form in the gallbladder.

Small stones are readily passed through the ducts into the intestine, causing attacks of biliary colic and spasm as they travel down the ducts. Medium sized stones may get just so far and become impacted. If this condition has persisted for some time the mucosa sloughs off and the stone is practically fused with the fibrous and muscular tissue of the duct. Large stones can not be passed, they are retained in the organ or, in certain instances, they may erode its wall and be discharged into the duodenum through an inflammatory fistulous opening. Under similar circumstances they may also be evacuated into the colon. In both cases fistulae may be established between the gallbladder and the intestinal tract. Impaction of stones in the cystic duct will lead to dilatation of the gallbladder if its wall is relatively healthy and distensible (i.e., before much fibrosis has occurred).

the lymphatic drainage and vascular supply lie largely in the loose tissue beneath the serosa. Small diverticula often extend from the mucosa through the muscularis; they are quasi-normal but probably occur most frequently in connection with the presence of stones. These are known as "Rokitansky-Aschoff" sinuses; first accurately described

by Morgagni in "De Sedibus et Causis Morborum" they should, by rights, bear his name rather than that of Rokitansky. Aschoff was the first modern pathologist to give them much attention.

PATHOLOGY

Metabolic Disturbances. The metabolism of the gallbladder is in a constant state of labile equilibrium. Slight changes in the concentration of cholesterol in the blood or bile or of the bile salts in the bile may bring about precipitations of one or the other; that of cholesterol seems to be the more usual. In other instances cholesterol may accumulate in the tips of the mucosal ridges, either in vacuoles in the epithelium or within phagocytes or "foam cells" which may form aggregations just beneath it; as the cholesterol increases true villi form and dangle in the lumen on threadlike pedicles, which are readily broken off. The mass thus liberated is then free to form the nucleus of a gallstone. Occasionally the gallbladder may present curdled masses of cholesterol resembling soft scrambled eggs. Cholesterol in and of itself cannot cause cholecystitis,



Remnants of intramural biliary calculus imprisoned within a Rokitansky-Aschoff sinus in wall of gallbladder. Note epithelial lining of sinus. This condition was first described by Morgagni.



Two large masses of macrophages containing cholesterol and lying upon mucosal surface of gallbladder. Such masses form dots and streaks of bright yellow that give the lesion its popular name "strawberry gallbladder."



Low powered view of wall of gallbladder in acute suppurative and hemorrhagic cholecystitis. Dark area at top replaces destroyed mucosa and comprises fibrin and debris. Beneath it are layers of muscle showing coagulation necrosis. Lighter lower half of field represents very edematous and inflamed serous layer, containing much delicate fibrin.

site of an acute flare up in a long standing inflammatory process. This is attested by the fact that the majority of "acutely inflamed" gallbladders (which are readily mistaken for the genuine article) prove to have thick, fibrous walls, vestigial musculature, and all the landmarks of chronic fibrous inflammation *plus* the hemorrhage, fibrinous exudate, and rather scanty leukocytic infiltration of the true acute variety. In addition one finds large numbers of eosinophils and plasma cells that indicate the presence of an underlying subacute inflammation. It is better to consider such specimens as examples of superimposed acute inflammation than of the primary variety.

These acutely inflamed organs may cause a rapidly developing peritonitis without having actually perforated, or they may perforate into the peritoneal cavity, into a neighboring viscus like the colon or duodenum, or into the substance of the liver. The inflammation may spread into the bil-

iary passages and into the liver. As a later result, scarring of the organ may bring about strictures or deformities like the so-called "hourglass" liver. Ulcers may persist in the mucosa.



Low powered view of wall of gallbladder in acute inflammatory episode superimposed upon chronic one—a not infrequent finding.

Impaction of stones further down is seldom complete; they act as ball valves and hence do not lead to distention of the gallbladder; furthermore, the organ is usually already fibrous and shrunken by the time stones begin to pass down the duct, so that it cannot dilate. One should not take Courvoisier's law too strictly, although it is true that distention of the gallbladder usually follows pressure from without the ducts such as that which results from carcinoma of the head of the pancreas, and does not follow the impaction of stones in those ducts.

Gallstones are not visible in the ordinary x-ray film unless they contain calcium, and sometimes masses of creamy mixtures of lime salts and bile may cast shadows that are mistaken for stones. It is possible, however, to visualize stones just as one visualizes the gallbladder itself: by means of the administration of tetra-iodophenolphthalein, after which the stones will become manifest as lighter areas in the shadow of the gallbladder.

Cholelithiasis, then, is not a simple process and is usually a part of infection of the gallbladder. Stasis without infection is not as frequent a cause, but it may be a factor in the case of obese and lazy individuals of sedentary habits and in pregnant women. Pregnancy inhibits much of the motility of the organ. Metabolic imbalance of the constituents of the bile may be the sole factor or a contributing one.

Inflammation. Cholecystitis, like appendicitis, is one of the commonest surgical diseases; like appendicitis, also, it offers a variety of acute, subacute, and chronic aspects. The gallbladder may become infected through the blood stream (probably the commoner route), through the biliary tree itself, or through the lymphatics. The frequent finding of a large, red, and inflamed lymph node at the neck of the organ (the "sentinel node") attests to the reality of the latter method. The causative organisms may be micrococci, or members of the *B. coli* group, or the typhoid bacillus which may linger in the organ long after the sub-

sidence of active typhoid fever. As in the appendix, obstruction of the ducts may aggravate infection or predispose thereto. Boyd points out that there is a striking difference between the bacteriology of appendicitis and that of cholecystitis; while bacteria teem in the former, there is little difference in the flora or the contents of acutely or chronically inflamed gallbladders.

ACUTE CHOLECYSTITIS. An "acute catarrhal cholecystitis" is rarely seen by the pathologist, as it tends to be self-limited and to disappear spontaneously. Acute suppurative cholecystitis is quite different from the analogous process in the appendix. The wall becomes thickened and brawny and is edematous rather than fibrous, dripping fluid on section. Hemorrhage is very prominent and suppuration much less so, as a rule. The organ is fiery red and the mucosal surface usually is covered with blood and adherent clots; there may be some small patches of fibrin on the surface of the serosa. Gallstones usually accompany the process; one seldom sees it without finding them. Portions of the wall may undergo softening and necrosis, so that perforation may take place, although this is relatively rare. The rôle of the Rokitansky-Aschoff sinuses as *loci minoris resistentiae* should be taken into account, for they often lead from the lumen to a point just beneath the serosa, and if inflamed they might afford a ready pathway for perforation.

In the microscopic picture hemorrhage is again an important constituent; while there is a purulent exudate into the wall of the organ, it usually lies in the subserosa, rather than in the muscularis, and abscesses are relatively rare. Of course, in some instances pus may exude into the lumen and collect there, particularly in obstructed organs. The subserosa presents extreme edema, and into this watery exudate much fibrin is precipitated—a factor that is important in subsequent fibrosis, as it readily undergoes organization by fibroblasts and sprouting capillaries. A great many specimens diagnosed as acute cholecystitis are actually the



Low powered view of wall of gallbladder in acute suppurative and hemorrhagic cholecystitis. Dark area at top replaces destroyed mucosa and comprises fibrin and debris. Beneath it are layers of muscle showing coagulation necrosis. Lighter lower half of field represents very edematous and inflamed serous layer, containing much delicate fibrin.

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Low powered view of wall of gallbladder in acute inflammatory episode superimposed upon chronic one—a not infrequent finding.

SUBACUTE CHOLECYSTITIS. In this condition the organ may appear to be almost normal, with little enlargement and with its wall neither thickened nor stiffened by fibrosis. Cholelithiasis may be present or absent. The interior of the organ is usually a rich orange brown with bright reddish areas mottling it. In about half the cases cholesterosis is present, with the characteristic strawberry marking. If neither stones nor cholesterosis are present the surgeon, upon opening and examining such a gallbladder, may be misled into thinking that he has made a mistake in operating. This, however, is not the case. The histologic picture reveals a fairly extensive exudate in which eosinophils are very prominent participants and the other cells are lymphocytes, plasma cells, or neutrophil polymorphonuclears. There is moderate edema, and the general architecture of the organ is not much altered. If cholesterosis is present the cholesterol will be found in vacuoles in the mucosa or within phagocytes collected in groups just beneath it.

CHRONIC CHOLECYSTITIS. This is by far the commonest lesion found at operation on the gallbladder; it may have begun insidiously and chronically and have continued in this vein, or it may be an outcome of repeated acute attacks, in which case it is not, strictly speaking, a chronic inflammation. There is no general rule for the gross appearance of the organ under these conditions except that it is almost invariably fibrous and has a thick wall that is tough on section. The fundus may be dilated and distended with bile and stones, or it may form a fibrous bag that is completely filled with stones and has little room for any bile. If there is a long-impacted stone in the neck the organ may be greatly enlarged, with thick and opaque walls. At the other extreme are those gallbladders which appear to be practically normal and have walls that are actually transparent, so thin are they; through these one may see many stones. Upon opening the organ it will be found to present an ap-

pearance that varies from that of an almost subacute process, with reddened and velvety mucosa, to one in which there is apparently no mucosa left and the organ appears to be a mere fibrous sac. Often there are trabecular markings on the inner surface, or there may be raised, stellate scars that form a pattern like the tracery of a Gothic ceiling. Sometimes ulcers present upon a thickened and somewhat polypoid mucosa, but they are rather uncommon.

Three histologic types of chronic cholecystitis may be recognized: the fibrotic, the cellular, and the glandular. The first is the commonest and reveals a marked increase in fibrous tissue and little evidence of active inflammation except for a scattering of lymphocytes about the vessels of the wall. The musculature may be hypertrophic or atrophic and replaced by fibrous scars. The very thin, chronically inflamed organs already alluded to reveal a wall so inert and acellular that one wonders why it has not sloughed and melted away. There is little mucosa left, the muscle is thin and atrophic, and only the fibrous tissue about the vessels seems to be alive.

The second type, the cellular, is more active; it exhibits definite aggregations of lymphocytes and plasma cells, with a few eosinophils and rather less fibrosis than the more fully developed instances of the fibrous type.

The third form (not at all as common as the other two) reveals a proliferation of the glandular elements of the mucosa with the development of numerous Rokitsky-Aschoff sinuses. These may often expand into roomy cyst-like chambers deep in the wall and contain masses of inspissated bile or small gallstones that are known as "intramural stones." It was the presence of these that first called Morgagni's attention to the sinuses in which they lay and which he correctly interpreted, with the use of a hand lens only, as microscopes had not yet come into use. Often enough the mucosa of these sinuses becomes destroyed and the concretions then lie in naked spaces in the

wall, surrounded by fibrous tissue. The mucosa is often almost polypoid in its exuberance and more closely resembles that of the neck of the organ where the glands of Luschka are situated. This is known as proliferating glandular cholecystitis, or "cholecystitis glandularis proliferans."



Wall of gallbladder in chronic proliferative glandular cholecystitis, showing great thickening of mucosa and atrophic muscular coat and fibrous wall invaded by adipose tissue

Whatever the type of chronic inflammation, the gallbladder may contain bile in amounts that vary from a few drops up to 40 cc or more, but if it has been obstructed this becomes either thin and watery and almost colorless, resembling saliva ("white bile"), or thick and extremely tenacious—so much so that it may be cut with the scissors like twine. If there has been infection in such an organ, the site of hydrops, the condition changes to one of empyema, with pus and mucus replacing the bile. As has already been noted, some gallbladders may

contain a greenish gray mass of material like rubber cement.

Tumors Although the gallbladder is composed of several forms of tissue that might give origin to tumors, these appear to arise chiefly from the mucosa, and even there they appear comparatively rarely.

Polyps may occasionally be observed, they closely resemble intestinal polyps in their appearance, both gross and microscopic. From these, or from the glands of Luschka, carcinomas may develop. These take two main forms: adenocarcinoma and epidermoid carcinoma.

ADENOCARCINOMA These are rarely found. Usually they arise in the neck of the organ; they may be relatively bulky, growing out into the lumen in a polypoid fashion, but more often they are infiltrating and scar-



Section from bulky carcinoma of fundus of gallbladder. Note excellent differentiation, which is misleading and is often noted in carcinomas of larger biliary and pancreatic ducts

rhous, invading the wall and causing its fibrosis. Microscopically, the polypoid tumors are much like the carcinomas of the intestinal tract in their appearance, those of the infiltrating variety show extraordinarily good differentiation, and when they metastasize they may appear almost like aberrant biliary ducts. This excellent differentiation is misleading, however, as they are invasive and malignant.

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pearance that varies from that of an almost subacute process, with reddened and velvety mucosa, to one in which there is apparently no mucosa left and the organ appears to be a mere fibrous sac. Often there are trabecular markings on the inner surface, or there may be raised, stellate scars that form a pattern like the tracery of a Gothic ceiling. Sometimes ulcers present upon a thickened and somewhat polypoid mucosa, but they are rather uncommon.

Three histologic types of chronic cholecystitis may be recognized: the fibrotic, the cellular, and the glandular. The first is the commonest and reveals a marked increase in fibrous tissue and little evidence of active inflammation except for a scattering of lymphocytes about the vessels of the wall. The musculature may be hypertrophic or atrophic and replaced by fibrous scars. The very thin, chronically inflamed organs already alluded to reveal a wall so inert and acellular that one wonders why it has not sloughed and melted away. There is little mucosa left, the muscle is thin and atrophic, and only the fibrous tissue about the vessels seems to be alive.

The second type, the cellular, is more active; it exhibits definite aggregations of lymphocytes and plasma cells, with a few eosinophils and rather less fibrosis than the more fully developed instances of the fibrous type.

The third form (not at all as common as the other two) reveals a proliferation of the glandular elements of the mucosa with the development of numerous Rokitansky-Aschoff sinuses. These may often expand into roomy cyst-like chambers deep in the wall and contain masses of inspissated bile or small gallstones that are known as "intramural stones." It was the presence of these that first called Morgagni's attention to the sinuses in which they lay and which he correctly interpreted, with the use of a hand lens only, as microscopes had not yet come into use. Often enough the mucosa of these sinuses becomes destroyed and the concretions then lie in naked spaces in the

wall, surrounded by fibrous tissue. The mucosa is often almost polypoid in its exuberance and more closely resembles that of the neck of the ovum where the glands of Luschka are situated. This is known as proliferating glandular cholecystitis or 'cholecystitis glandularis proliferans'.



Wall of gallbladder in chronic proliferative glandular cholecystitis, showing great thickening of mucosa and atrophic muscular coat and fibrous wall invaded by adipose tissue

Whatever the type of chronic inflammation, the gallbladder may contain bile in amounts that vary from a few drops up to 40 cc or more, but if it has been obstructed this becomes either thin and watery and almost colorless, resembling saliva ("white bile"), or thick and extremely tenacious so much so that it may be cut with the scissors like twine. If there has been infection in such an organ, the site of infection, the condition changes to one of suppuration with pus and mucus replacing the bile. It has already been noted, in a gallbladder removed

for a greenish-yellow color of external like rubber cement.

Tumors. Although the gallbladder is composed of several forms of tissue that might have origin to tumors, these appear to arise chiefly from the mucosa and even there they appear comparatively rarely.

Polyps may occasionally be observed; they closely resemble intestinal polyps in their appearance both gross and microscopic. From these, or from the glands of Luschka, carcinomas may develop. These take two main forms—adenocarcinoma and epidermoid carcinoma.

ADENOCARCINOMA. These are rarely found. Usually they arise in the neck of the organ; they may be relatively bulky, growing out into the lumen in a polypoid fashion, but more often they are infiltrating and scar-



Section from bulky carcinoma of fundus of gallbladder. Note excellent differentiation, which is misleading and is often noted in carcinomas of larger biliary and pancreatic ducts.

rhous, invading the wall and cutting its fibrous. Microscopically, the polypoid tumors are much like the carcinomas of the intestinal tract in their appearance, those of the infiltrating variety show extremely good differentiation, and when they metastasize they may appear almost like distant biliary ducts. The excellent differentiation is not to be taken as a guide, for the same is seen in other malignant tumors.

SUBACUTE CHOLECYSTITIS. In this condition the organ may appear to be almost normal, with little enlargement and with its wall neither thickened nor stiffened by fibrosis. Cholelithiasis may be present or absent. The interior of the organ is usually a rich orange brown with bright reddish areas mottling it. In about half the cases cholesterosis is present, with the characteristic strawberry marking. If neither stones nor cholesterosis are present the surgeon, upon opening and examining such a gallbladder, may be misled into thinking that he has made a mistake in operating. This, however, is not the case. The histologic picture reveals a fairly extensive exudate in which eosinophils are very prominent participants and the other cells are lymphocytes, plasma cells, or neutrophil polymorphonuclears. There is moderate edema, and the general architecture of the organ is not much altered. If cholesterosis is present the cholesterol will be found in vacuoles in the mucosa or within phagocytes collected in groups just beneath it.

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present formidable problems which are being successfully met and overcome

In connection with these tumors the surgical pathologist is usually called upon to decide, after inspecting frozen sections of biopsies, whether a given instance of obstructive biliary obstruction is due to (1) carcinoma of the head of the pancreas, (2) carcinoma of the ampulla of Vater, (3) carcinoma of the duodenum in the region of the papilla, or (4) duodenal ulcer with inflammatory induration of the head of the pancreas as a cause of the pressure upon the common duct

PANCREAS

Unlike most other organs, the pancreas exhibits no developmental defects of note, unless these accompany such marked aberrations in development that a monster results. Pancreatic tissue, however, may be displaced to a variety of situations, little islands of pancreas may be found in the wall of the stomach or in a Meckel's diverticulum, for example

Vascular Changes In the pancreas these are of relatively little import, although arteriosclerosis may be so marked as to bring about a fibrosis, of which we shall speak later. In instances of hypertension it is quite common at necropsy for the pathologist to examine the pancreas carefully for arteriolar changes, which stand out prominently in that organ

PANCREATIC APOPLEXY Extensive hemorrhage may disrupt and largely destroy the organ without any adducible evidence of inflammation. In a subject who has died with typical signs of acute pancreatitis one will find an organ that is riddled with hemorrhages or actually disrupted by them, without giving evidence of any other pathologic changes. Several cases of this type have been known to develop within a short space of time in a large city, as though there might be some common cause, but this has not been discovered and the etiology of the accident remains mysterious. It is sup-

posed to be unconnected with arteriosclerosis

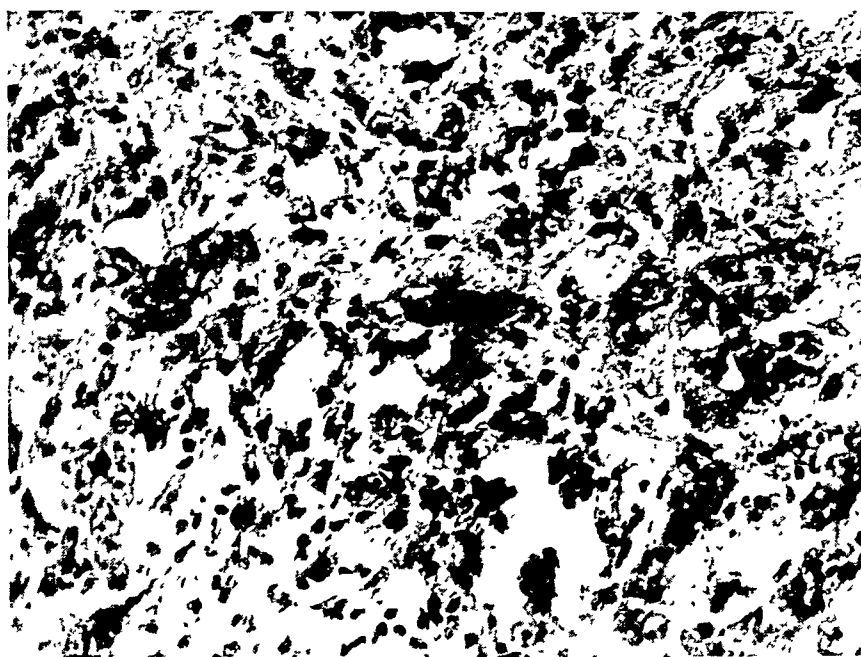
Pancreatitis ACUTE PANCREATITIS Titz's original division of this disease into hemorrhagic, gangrenous, and suppurative types probably depends upon three advancing stages in the same process, which occasions a fulminating attack of excruciating epigastric pain that bores into the back and simulates perforating duodenal ulcer. The patient is found to be prostrated and in shock a few hours after having been in apparently good health, possibly following a hearty meal. When the organ is exposed it might be described as being "shot to pieces", it shows many areas of hemorrhage, it is crumbling and friable so that it cannot be removed by the surgeon, who must content himself with draining the area. Depending upon the stage in its progress, hemorrhage, necrosis, or actual suppuration may be found. The peritoneal fat in the neighborhood is flecked with small, whitish-yellow, opaque, and firm areas that look like bits of soap, and in fact they are much like soap, the escape of lipases from the destroyed pancreas saponifies the neutral fats of the adipose tissue.

Microscopic examination is not particularly satisfying, for the afflicted pancreas has become a mass of hemorrhage and necrotic pancreatic tissue, with much fibrin deposited in the tissue and an exudate of polymorphonuclears that increases according to the stage of the process. The fat necroses appear very much like adipose tissue that has undergone a chemical change wherein the cells have become semi-opaque masses of slightly granular material that stains very poorly. At the margins of these areas are many fat phagocytes or lipophages which have taken up droplets and bits of the necrotic fat so that they are filled with granules or droplets, as the case may be.

The etiology of pancreatitis is apparently a matter of a backflow of bile into the pancreas through one of its secretory ducts, particularly that of Wirsung. Opie's theory that there is blockage of the papilla of Vater

EPIDERMOID CARCINOMA. This type of carcinoma is well known to pathologists on account of the fact that it was chiefly in the gallbladder that metaplasia of epithelium from a glandular to an epidermoid type was first studied and noted. It is now known that this can occur also in other localities, such as the pelvis of the kidney, the ureter and urinary bladder, the breast,

esses, and various forms of obstruction, including parasites. After cholecystectomy the stump of the cystic duct may become dilated and transformed into a small travesty of the gallbladder in an apparent attempt to compensate for its loss; stones will form in this, and they are usually recognizable as duct-stones on account of their softness and reddish-brown color.



Incipient adenocarcinoma of gallbladder developing in a phrygian cap. Its cells form dark groups in lighter background of inflamed connective tissue.

and other organs. From such a metaplastic epithelium in the gallbladder epidermoid carcinomas may be produced. In spite of our familiarity with them we seldom see them. They resemble epidermoid carcinomas in general and may show a predominance of acanthotic cells with the typical intercellular fibrils or bridges interconnecting them. The best treatment, naturally, is a wide excision of the gallbladder and a careful search for any metastatic foci in neighboring lymph nodes, particularly that at the neck of the organ.

BILIARY DUCTS

These ducts more or less recapitulate the pathologic alterations noted in the gallbladder, and one may note changes due to metabolic disturbances, inflammatory proc-

Tumors. These are essentially similar to those of the gallbladder and exhibit the same general types. They are most apt to develop in the ampulla of Vater and extend up and down the duct, effectually blocking the common duct at and above the papilla. They show the same good degree of differentiation that is exhibited by the scirrhous type of adenocarcinoma mentioned in the case of the gallbladder. Their eradication involves complicated surgery, as the continuity of the common duct cannot be established and an outlet for bile and pancreatic secretion must be provided. As this is not a textbook of surgery we cannot go into this, but the anastomosis of the gallbladder and intestine, or stomach, together with the removal of the ducts, the head of the pancreas, and most of the duodenum

of Cecil Carcinomas may occur in any part of the organ, but most frequently they are found in the head, where they interfere with biliary secretion and provoke severe jaundice of the obstructive type. Carcinoma is apt to follow pancreatic sclerosis, even as it was seen to be associated with cirrhosis. Ewing gives its distribution in the organ as 158 diffusely involving the whole

and intestine to cause perplexity in some instances, particularly if it is not of the well differentiated variety. The simple type of carcinoma that arises from the cells of the parenchyma may resemble this to a certain extent, or it may be composed of rounded, ovoid, or fusiform cells that may be grouped into rosettes and may mislead the pathologist into mistaking it for a sympathoblast



Carcinoma arising in ducts of pancreas. It is well differentiated and misleadingly innocent looking. This is often true of carcinomas of pancreatic and biliary duct trees.

pancreas, 156 limited to the head, 28 in the body, and 12 in the tail. These tumors metastasize early.

HISTOLOGIC TYPES. There are two of these: those which arise in the ducts and are probably more commonly found in the head and body of the organ, and those which originate in the parenchyma and may be so undifferentiated as to resemble reticulum celled sarcoma, or fibrosarcoma. This sarcomatoid type is more often observed in the body and tail, particularly the latter. The duct celled type is usually well differentiated and resembles pancreatic ductile tissue closely enough to be recognized in metastases with some degree of assurance. However, it does bear enough similarity to carcinomas of the biliary tree

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ISLET CELLED TUMORS (NESIDIOBLASTOMAS). Only comparatively recently have

by a stone rests upon the fact that pancreatitis usually occurs in elderly and obese individuals and in association with cholelithiasis. That a stone is not always demonstrable may mean no more than that it has moved on. Boyd quotes Rich and Duff, who maintain that unactivated pancreatic juice escapes into the stroma of the gland behind an obstruction in the duct caused by "metaplasia and heaping up of the epithelium" which blocks the lumen; such ruptures may take place into the pancreas, however, without causing pancreatitis.

CHRONIC PANCREATITIS. This chronic interstitial fibrosis, which Opie divides into interlobular and interacinar types (similar respectively in their distribution to the Laënnec and Hanot types of cirrhosis), is a condition that interests surgical pathologists chiefly in so far as it causes an almost stone-hard pancreas and, when present in the head of the organ, may simulate carcinoma. Surgeons frequently take biopsies from such organs in an endeavor to rule out the presence of carcinoma; therefore these are of importance to both patient and operator. A steadily increasing fibrosis compresses the parenchyma and is more often interlobular than interacinar. This has been attributed to chronic poisoning by heavy metals, alcohol, and so on; chronic obstruction of pancreatic ducts may also be to blame. Senility and arteriosclerosis are so often observed that they are given some emphasis by a number of authorities.

SUBACUTE FOCAL PANCREATITIS. This is not often mentioned, but one does frequently find areas of acute inflammation, with edema and possibly a chronic exudate and fibrosis of an early type, in the head of the pancreas. This is usually attributable to the perforation or partial perforation of ulcers of the stomach or duodenum which, because they are inflamed, introduce inflammation (and possibly infection) into the area upon which they impinge. When this state of affairs involves a duodenal ulcer and the head of the pancreas it may set up a chain of symptoms pointing to carcinoma

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Pancreatic Cysts. There are two types of pancreatic cyst: the true and the false.

TRUE CYSTS. These may again be subdivided into those that result from obstruction to the ducts (retention cysts) and those that are primary cystadenomas; intermediate between these are the congenital cysts that are much like those of the kidney and liver in their multiplicity. This last type may be dismissed with the remark that it is rare and attributable to stenosis or atresia of the ducts through faulty development. The obstructive cysts that develop in later life are also due to occlusion, but in this instance calculi, or scars and fibrosis from inflammation, as well as outside pressure by neighboring tumors or areas of inflammation, may be the etiologic factors. Such cysts contain a clear, glairy fluid like ropy saliva; their walls are formed by those of the dilated ducts in which they arise.

Cystadenomas show a very abundant overgrowth of their lining and the formation of numerous papillae. They may be single or multiple and are rare. Cecil has described small pea-sized cysts developing from islets of Langerhans.

FALSE CYSTS OR "CYSTOIDS." These are usually formed outside of the organ, often in the lesser omental sac; as they usually contain brownish, muddy material and cholesterol it would seem that they result either from trauma or the encapsulation of areas of hemorrhage such as have been described in connection with pancreatic apoplexy. Thus they probably represent "blood cysts" like those in thyroid adenomas, certain tumors in which hemorrhage is copious (like the hypernephroid growths), or hemorrhagic follicular ovarian cysts.

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tumors of islet cells been recognized; the majority seem to be noncancerous. When present they occasion grave disturbances in the insulin secretion, with production of hyperinsulinism that is relieved by the exhibition of sugar in some form. Most of them appear to be composed of beta cells.

color reaction may be reversed; the islet cells then stain green.

Laidlaw and Murray found that tumors of islet-cell origin reacted in exactly this manner. They proposed the name "nesidioblastoma," which they considered more compact than "islet-cell carcinoma of the



Carcinoma of tail of pancreas metastatic in choroid plexus over cerebellum. Note resemblance of its cells to those of a sarcoma. Structure at center is the stroma of a choroid villus. (From Foot, Carter, and Flipse, *Amer. Jour. Med. Sci.*, 1924.)

The malignant type acts like a carcinoma and may be considered to be one; it is usually single, which is fortunate from the surgical standpoint, but it may be multiple. Microscopically these tumors resemble the islands of Langerhans in their general appearance, but one should not make a diagnosis on this alone, as some of the simple type of parenchymatous carcinomas have been mistaken for islet-cell tumors and described as such in publications. The parenchymatous pancreatic cells take a green stain with Benseley's method, while the islet cells are found to contain many bright-red granules; by appropriate treatment the

pancreas" ("nesidion" in Greek means "islet"). These are tumors which may be diagnosed by clinical means and studies on the blood-sugar concentration; the hypoglycemia they produce disappears after their removal.

SARCOMA. Because of its similarity in appearance to that of the carcinoma simplex of the pancreatic parenchyma it is not too easy to recognize sarcoma; as a matter of fact it is a rare tumor in this situation. Ewing accepts two possible types as truly sarcomatous: a fusicellular fibrosarcoma and a lymphosarcoma that might arise in any organ.

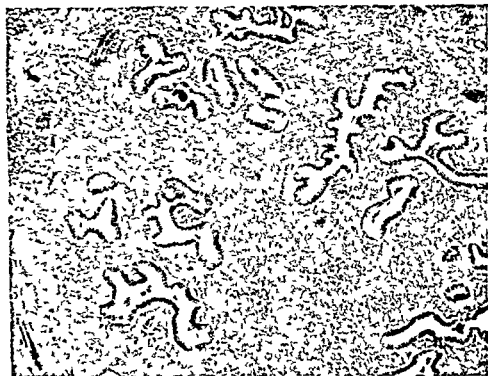
cent In such kidneys the pelvis may be fused or separate and the ureters quite anomalous, passing over the isthmus to the bladder If the kidneys fail to ascend to their normal position "dystopia," or congenital displacement, may result, this is more usual in the left than in the right organ

ENDOMETRIAL INCLUSIONS An extremely rare lesion of the kidney, probably based

represent an endometrial explant, but in the absence of endometriosis in the one patient observed, this seems unlikely

Cysts There are two types of renal cyst, neither of which should be considered as neoplastic, one is acquired, the other congenital

ACQUIRED CYSTS These may be single (measuring about 2 to 4 cm in diameter) or multiple The latter, which are situated



Typical endometrial tissue from a wedge that invaded the midportion of a kidney This is the only instance of this developmental defect on record

upon a developmental anomaly, has been reported in one instance from our hospital and is mentioned here because there is no literature on the subject as yet This anomaly takes the form of the interposition of a wedge of endometrial tissue between the poles of the kidney (See Marshall) Microscopically it has the appearance of normal endometrium which might have developed from included mullerian tissue before the metanephros capped the ureteral bud An other possibility is that portions of the metanephros might have mullerian potentiality which brought forth endometrial rather than renal tissue Lastly, it might

beneath the capsule, are usually smaller than the solitary variety, measuring from a few millimeters to 1 cm in diameter They are filled with clear fluid and have thin walls that are usually torn when the capsule is stripped from the kidney, although they may be more deeply situated in the cortex Their etiology appears to be connected with obstruction of a nephron by fibrotic, inflammatory, or other changes In the case of nephrosclerosis the cysts may attain considerable size and are usually multiple

CONGENITAL CYSTS It has long been claimed that the single simple cyst of the renal cortex is a developmental anomaly

15

Urinary System

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TUMORS OF RENAL PARENCHYMA

EXAMINATION OF URINARY SEDIMENTS
FOR NEOPLASTIC CELLS

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CALCULI AND FOREIGN BODIES

PARASITES

INFLAMMATION

DIVERTICULA

TUMORS

URETHRA

CONGENITAL ANOMALIES

INFLAMMATION

TUMORS

PENIS

CONGENITAL ANOMALIES

INFLAMMATION

PEYRONIE'S DISEASE

TUMORS

KIDNEYS

The kidneys develop from the lowermost portion of the primordial renal tissue known as the "metanephros." This becomes united to the ureters, which grow up from the hindgut and fuse with this "afterkidney," supplying it with its collecting tubules and pelvis. The pronephros of early embryonal life plays an unimportant rôle in the development of the human kidney. The mesonephros, after serving as an excretory organ throughout a considerable part of embryonal existence and constituting the upper pole of the "renal blastema" (a term much used by Ewing), disappears. Before doing so, however, it leaves between itself and the site later to be occupied by the kidney a block of tissue known as the "mesoblastema" which probably figures importantly in the production of a number of embryonal tumors of the perirenal area and the gonads. Thus the kidney is, in the

main, mesoblastic, while its calices, pelvis, and ureter are entodermal.

Congenital Anomalies. Unilateral agenesis of the kidney is not uncommon, with the organ that is developed on one side becoming correspondingly hypertrophied and serving in the capacity of the usual paired organs. Naturally, bilateral agenesis of the kidney is incompatible with life and does not figure in surgical pathology. Neither does bilateral hypoplasia, which is an underdevelopment of the kidneys. Unilateral hypoplasia is occasionally observed and is compensated for by corresponding hyperplasia of the other organ. Occasionally the lower poles of the kidneys fuse across the midline, being joined by an isthmus and forming a horseshoe kidney which, when it is observed, is so impressive that it is surprising to find that this anomaly has an incidence (Keyes, cited by Karsner) of only 30 in 21,218 autopsies, or about 0.14 per

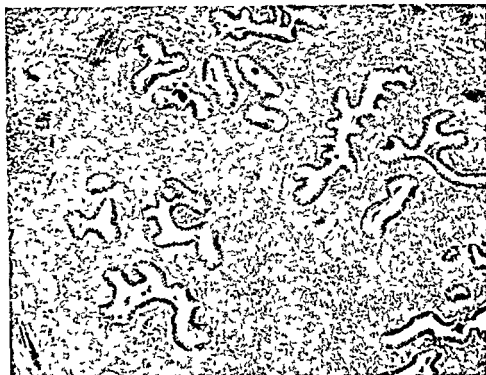
cent In such kidneys the pelvis may be fused or separate and the ureters quite anomalous, passing over the isthmus to the bladder If the kidneys fail to ascend to their normal position "dystopia," or congenital displacement, may result, this is more usual in the left than in the right organ

ENDOMETRIAL INCLUSIONS An extremely rare lesion of the kidney, probably based

represent an endometrial explant, but in the absence of endometriosis in the one patient observed, this seems unlikely

Cysts There are two types of renal cyst, neither of which should be considered as neoplastic, one is acquired, the other congenital

ACQUIRED CYSTS These may be single (measuring about 2 to 4 cm in diameter) or multiple The latter, which are situated



Typical endometrial tissue from a wedge that invaded the midportion of a kidney This is the only instance of this developmental defect on record

upon a developmental anomaly, has been reported in one instance from our hospital and is mentioned here because there is no literature on the subject as yet This anomaly takes the form of the interposition of a wedge of endometrial tissue between the poles of the kidney (See Marshall) Microscopically it has the appearance of normal endometrium which might have developed from included müllerian tissue before the metanephros capped the ureteral bud Another possibility is that portions of the metanephros might have müllerian potentiality which brought forth endometrial rather than renal tissue Lastly, it might

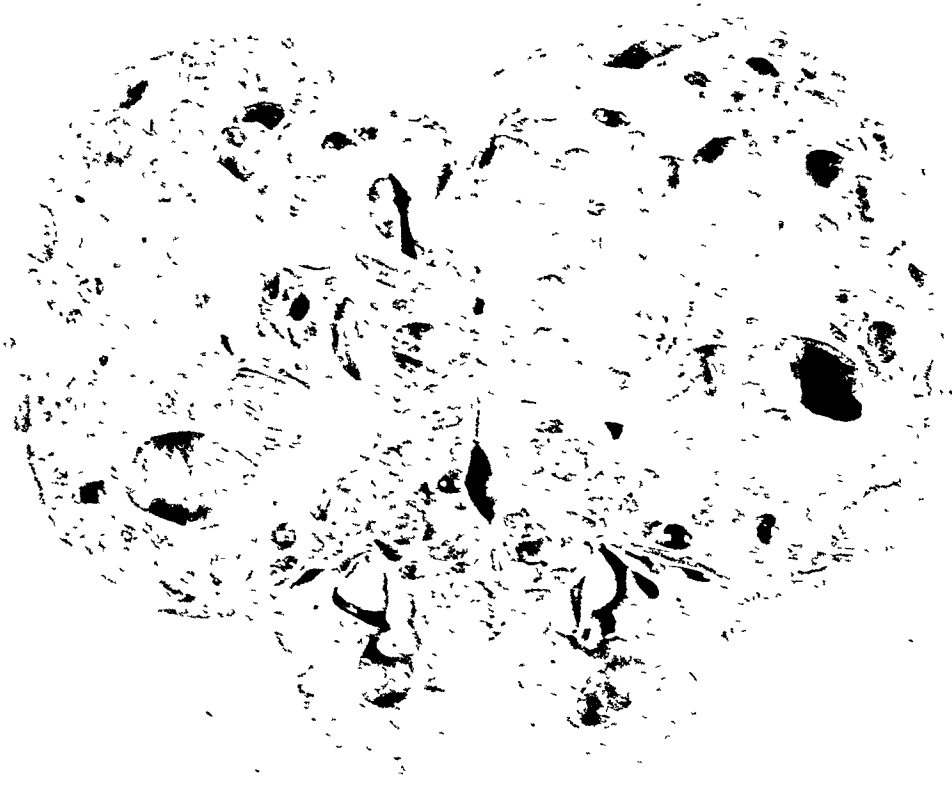
beneath the capsule, are usually smaller than the solitary variety, measuring from a few millimeters to 1 cm in diameter They are filled with clear fluid and have thin walls that are usually torn when the capsule is stripped from the kidney, although they may be more deeply situated in the cortex Their etiology appears to be connected with obstruction of a nephron by fibrotic, inflammatory, or other changes In the case of nephrosclerosis the cysts may attain considerable size and are usually multiple

CONGENITAL CYSTS It has long been claimed that the single simple cyst of the renal cortex is a developmental anomaly

and congenital, although it is difficult to decide definitely whether or not this is so.

CONGENITAL POLYCYSTIC KIDNEY. The multiple cysts that convert the kidneys into spongy structures composed of innumerable bladder-like cavities are of varying size and are found throughout their substance. This

The cysts vary from 4 to 10 mm. in diameter. As a rule they are filled with a clear fluid or a gelatinoid substance which, on chemical analysis, is found to be similar to tubular urine. Their walls are thin, and under the microscope they are found to be composed of cuboidal epithelium supported



Kidney of young child, showing half of organ replaced by huge multi-ocular cyst. This resembles congenital polycystic kidney, but fails to involve entire organ and spares contralateral kidney.

condition is known as "congenital polycystic kidney," for the cysts are definitely congenital. They arise often in conjunction with similar cysts in the liver, less frequently with those of the pancreas and spleen. Kidneys thus affected may attain a weight of 1 Kg. apiece. In about two-thirds of the cases the patients possess sufficient functional renal parenchyma in these kidneys to carry them along into middle age, but then the equilibrium becomes lost. Any severe intercurrent disease will be enough to upset this and to bring about renal failure and uremia, which kills the patient.

on a thin fibrous wall. Some of them may contain atrophic or abortive glomeruli. The cause of the lesions has long been discussed and disputed. An early explanation depended upon a failure of fusion of mesodermal with entodermal elements during the "capping" process, the hypothesis being that the former secreted urine but had no outlet for it. Another theory, cited by Karsner, is that there is isolation of the first generation of convoluted tubules formed by the mesoblast. This results from detachment of these from the collecting tubules. Filtration takes place, but there is inadequate absorption of the urine farther down

the nephron, so that gradual dilatation results. The glomeruli atrophy and disappear in many areas of the cortex.

Degenerative Lesions, Trauma Degenerative conditions, such as amyloidosis, together with the pathology of trauma, require little attention here. The kidneys may be traumatized by crushing injuries, falls, and similar accidents, and there may be subcapsular and perirenal hemorrhage as well. In the latter case hemorrhagic cysts may be produced, with the blood undergoing decomposition and leaving a thick walled cyst filled with a thin, brownish fluid in which much cholesterol is seen in the form of glistening golden crystals that are quite typical.

The late ischemic lesions brought about by the taking of blood in the renal vessels and changes in the tubular epithelium attributable to the attempted excretion of the hemoglobin thus set free have been admirably described by Lucke in connection with his recent investigations into the pathology of "crush injury." The point that should be stressed here is that the crushing injury takes place elsewhere (let us say in a leg or arm that has been pinned down by falling debris), it has nothing to do with crushing the kidneys themselves. The lesion is only hypothetically connected with surgical pathology.

Infections ACUTE SUPPURATIVE NEPHRITIS Hematogenous Infection The "surgical kidney" is usually part of a generalized infection, most commonly by some strain of staphylococcus. Small multiple abscesses dot the parenchyma of the organ and vary from milium size to a diameter of a few mm.

Acute Pyelonephritis This is much more usual and results from the upward spread of an infection that may have ascended from the bladder or invaded the ureter from the intestinal tract. Lymphatic transmission of such an infection is very important, as is focal hematogenous spread. As a result of pyelitis (see later) the kidney becomes secondarily infected and inflamed.

It is swollen, heavy, and of a variable consistency. Its capsule strips readily, revealing a very much mottled subcapsular surface, perhaps studded with small yellowish abscesses. The cortex is swollen and mottled on its sectioned surface, and the medulla may be vividly streaked with bright red striae alternating with yellow lines of pus.

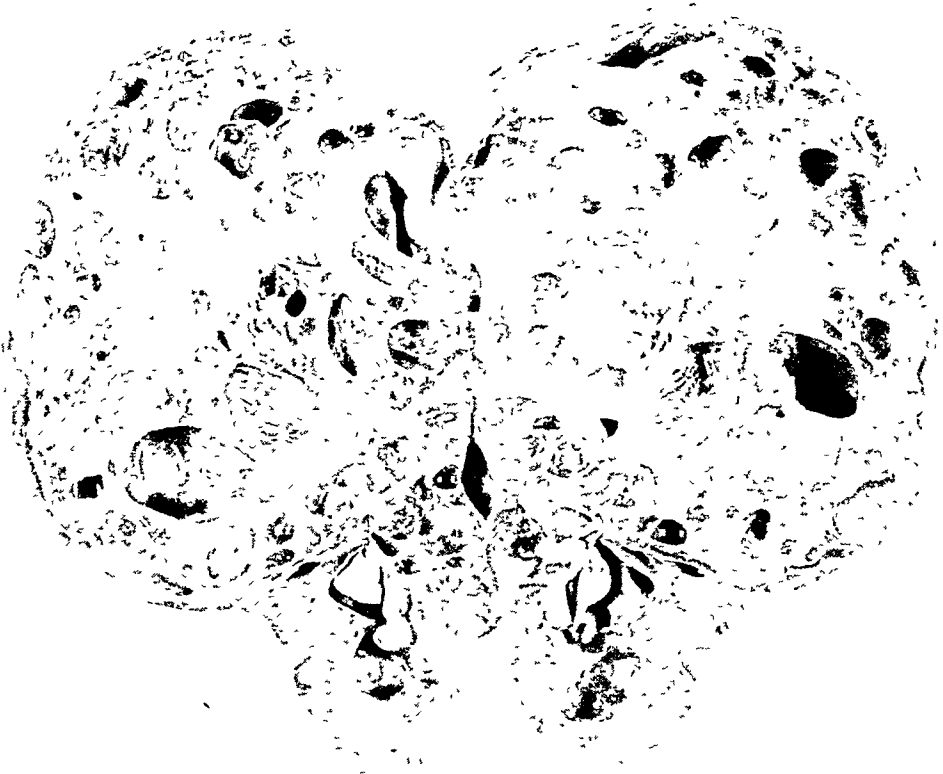
Microscopically the organ shows pus in the collecting tubules and possibly further out into the cortex. Casts are present in some portions of the organ, absent in others that are less affected. The process may not be particularly generalized, sometimes it is concentrated in one pole or about the pelvis. This applies particularly to the lesion when it is associated with calculi. Naturally, the pelvic mucosa will exhibit acute inflammation, possibly with some fibrin on the surface of its epithelium and general loosening and destruction of some of its cells. The interstitial stroma of the kidney may exhibit scattered collections of polymorphonuclear leukocytes, or small abscesses. Usually the process is most marked in the vicinity of the pelvis and fades off as it proceeds outward toward the capsule. On occasion this may be penetrated, and a perinephric abscess may be formed.

Much has been written on the subject of the mechanism of ascending infection, and a good deal of experimental work has been done to elucidate the question. There are three possibilities: the organisms may travel in the ureteral lumina, in the perireteral lymphatics, or in the blood stream. The old claim that bacteria cannot swim upstream has been countered by the discovery that pressure upon the bladder may cause a reflux of urine that might very well carry them up into the renal pelvis. Experiments on animals with ligated ureters have demonstrated that ascending infections are sometimes possible of accomplishment, and injections of India ink have indicated that the lymphatics may carry particulate matter from the bladder to the renal pelvis. It is difficult to understand how organisms entering the circulating blood might be selec-

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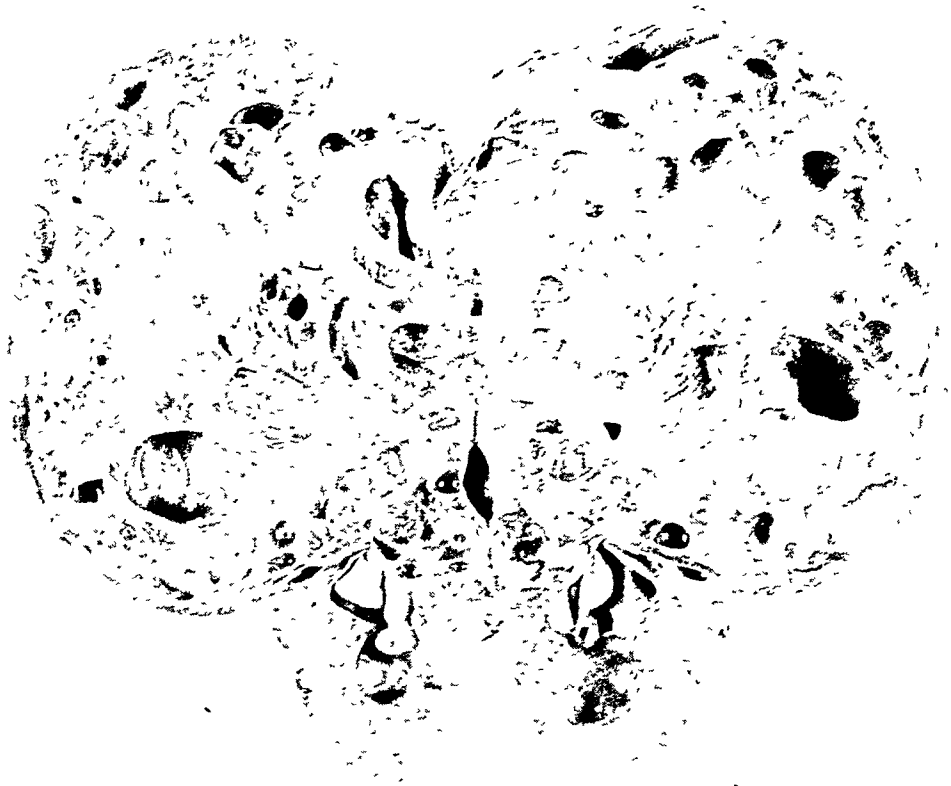
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SUBACUTE PYELONEPHRITIS. This usually represents a continuance of an acute process that shows phases of exacerbation and remission. It results in the destruction of areas in the organ that are then replaced by cicatricial tissue which produces lobulated kidneys with deep and pitted scars that resemble those of infarcts. Sections of these, however, show them to be shallow and flat, rather than deep and conical with their apices oriented toward the medulla, as would be the case with scars of true infarcts. The scattered foci of fibrosis that alternate with comparatively normal areas involve the capsule, fusing with it and causing it to adhere and strip with difficulty.

Microscopic sections of such kidneys reveal a good deal of pathologic alteration of the interstitial tissue which may be diffusely infiltrated with lymphocytes, or by groups of these in a follicular form. One finds the comparatively normal areas alternating with wedges of renal tissue that exhibit interstitial infiltration and fibrosis and atrophy of the tubules with a typical cystic alteration in which these become interrupted at intervals. The occluded portions then become distended and constitute microcysts that are filled with a hyaline material so closely resembling thyroid colloid that they are often miscalled "colloid cysts." One of these areas is readily mistaken for a bit of thyroid by an inexperienced observer.

Concomitantly with these changes, particularly in unilateral lesions, the vessels may undergo considerable sclerosis, hyper-

trophy, or necrosis; both arteries and arterioles share in this alteration. The arteriolar participation in this may lead to clinical symptoms and signs of hypertension. Glomeruli in the affected areas usually undergo fibrous obliteration. Thus a section from such a kidney should exhibit irregular areas of fibrosis, lymphocytic infiltration of the interstitial tissue, fibrosis of glomeruli, possible areas of acute inflammation, and pus in occasional tubules. Hyaline casts resembling thyroid colloid and sclerosis of both arteries and arterioles will accompany these. Such kidneys, if diagnostic procedures indicate that only one of the patient's organs is involved, are often removed as a remedial measure in hypertension. Biopsies from kidneys, which are often taken during a splachnicectomy for the relief of hypertension, usually reveal this type of lesion.

PERINEPHRIC ABSCESS. Acutely infected kidneys often cause inflammation of the perirenal tissue with the formation of perinephric abscesses which may attain considerable size and importance. They may accompany infections in neighboring organs also, such as the appendix, or they may result from a pyemic infection and arise independently of any local abscesses in the kidney or neighboring organs. After they have been drained, fistulae often persist and constitute a source of frequent although not very illuminating biopsies.

INFECTIOUS GRANULOMAS. *Tuberculosis.* This may have a distribution and an underlying mechanism of infection very similar to those of pyogenic organisms, but it is usually more massively destructive than they are. The hematogenous form of tuberculosis is usually part of generalized miliary tuberculosis. It needs no further comment here. Karsner stresses the intratubular form of tuberculosis that follows the passage of bacilli through the glomerular loops and produces long, streaked tubercles within the tubules. Such an infection may spread to the pelvis and then loop back along collecting tubules in a fashion simulating an in-

fection that began as an ascending one. In this form of the disease one pole of the kidney may be streaked and dotted with small conglomerate tubercles that may be situated near the cortex.

The ascending form of tuberculous infection usually begins in the prostate, seminal vesicles, or epididymides and works its way up the ureters, occasionally occluding them to such an extent that they become distended. When it reaches the kidney a tuberculous pyelonephritis is initiated, working outward and causing large areas of caseous necrosis in the vicinity of the calices. Mixed infection is not uncommon, and the resulting abscesses bring about marked loss of renal substance, hence this form of lesion is called "phthisis renalis." Naturally, such destruction is accompanied by attempts at healing which result in conspicuous fibrosis. The kidney may be reduced to a mere bag of pus contained in a thin shell of cortex and capsule. Its contents are an unlovely mass of chalky caseous material in which numerous calculi may be encountered. Such a nasty looking lesion should be foul smelling, but although that is true of most of the pyogenic pyonephroses, many of the tuberculous variety are practically odorless.

Microscopic examination of the tuberculous kidney reveals a picture similar to that of subacute pyelonephritis, except that typical tubercles and areas of tuberculous caseation constitute the underlying lesion.

Other Infectious Granulomas. Syphilis and actinomycosis are too rarely encountered in surgery to be of particular interest here.

Nephritis. The only form of nephritis that touches at all closely on surgical pathology is the chronic glomerular type, in this there may be changes in the arterioles leading to hypertension that occasions surgical intervention such as decapsulation or splachnicectomy, in the course of these operations biopsies may be taken for diagnosis. Such a kidney will show reduction in size and weight, although it may be un-

changed. Granular and nongranular forms of the lesion are recognized, they depend largely upon the amount of fibrosis and resulting puckering or scarring of the stroma. The color of the kidney varies from mottled yellow on gray to mottled yellow on red. The cortex is slightly reduced in thickness, and its markings are jumbled and obscure, in the granular form the cortex shows irregularity in its thickness.

As the name implies, the microscopic lesions are most marked in the glomeruli, some of which are more affected than others. There is fibrosis of the capsule, followed by fibrosis of the tufts until the entire glomerulus becomes converted into a hyaline, fibrous spheroid. Multiplication of the epithelial lining cells of Bowman's capsule may be prominent, if it is, there are crescentic masses of these cells within the fibrous capsule. They are more often noted in the subacute stages that follow the extracapillary or subcapsular type of acute lesion. Tubular changes vary a great deal. The epithelium shows granular degeneration, fatty infiltration, or even necrosis and desquamation. Regenerative phenomena may lead to the production of small adenomatoid areas or cysts. The arterial vessels may exhibit sclerosis, and it is often difficult to decide whether this is a result of the process, whether it develops concomitantly, or whether the arteriosclerosis may underlie the glomerular lesion.

Nephrosclerosis. Arterial nephrosclerosis is unassociated with hypertension, so that it may be omitted here, arteriolar nephrosclerosis, on the other hand, is definitely associated with this clinical entity, and certain surgical procedures are aimed at alleviating the symptoms. A distinction is made between arteriolar *disease* of the kidney, which produces no gross distortion of its architecture, and arteriolar *nephrosclerosis*, in which there is such distortion. The distinction is a fine one, for although gross changes are not visible, the microscope reveals arteriolar sclerosis in the kidney of the former condition and there is

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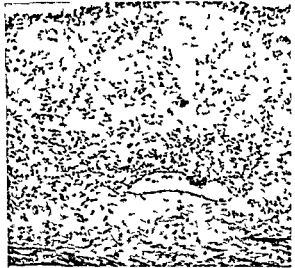
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are two points of normal narrowing of the ureters—one at their emergence from the renal pelvis and the other at their entrance into the base of the trigone of the bladder. These may be congenitally accentuated to a point where one can speak of congenital stricture, such strictures, of course, may lead to back pressure and result in hydronephrosis. There may be anomalies in the course of the ureters. The normal points of narrowing are naturally those at which stones usually become impacted during their passage from the kidney to the bladder. The pelves and calices may often show variations from their normal architecture, the pelves sometimes being divided into two main branches and the calices varying a good deal in their degree of complexity. All these malformations are readily diagnosed by intravenous pyelography, aided by retrograde injection of radio opaque solutions into the ureters.

Inflammation. ACUTE CALICITIS, PYELITIS, AND URETERITIS. Any portion of the excretory ducts may become acutely infected, usually by members of the dysentery group of bacilli, the routes of infection have already been indicated. There are redness, swelling, and visible fibrinous exudate on the surface. The microscope reveals destruction of the epithelium with infiltration by polymorphonuclear leukocytes into this and the loose connective tissue that underlies it. The inflammation is usually characterized clinically by a febrile reaction that is out of all proportion to the pathologic features, with high fever, shaking chills, and a high leukocyte count. Pyelitis is common among children and is often masked by concomitant gastroenteric symptoms, it is more common in females of all ages than in males. If it extends into the calices, as it is almost bound to do, pyelonephritis is the natural consequence. Pyelitis is believed to play a very important part in the later production of renal calculi, which may appear years after the acute phase of the infection has subsided. If the process continues the pelvis may

become distended with pus and the calices may follow suit, a lesion known as "pyonephrosis" results. This is a state resembling hydronephrosis (see below), with pus replacing the urinary elements of that condition.

CHRONIC CALICITIS, PYELITIS, AND URETERITIS. This is usually a clinically (rather than pathologically) chronic process, as it represents a continuing acute or subacute



Typical view of chronic pyelitis. Mucosa has been much thinned out. Note chronic inflammation in supporting tissue.

inflammation plus the histologic elements of chronic inflammation. As a result of this and the presence of calculi, the epithelium and its supporting tissue respond with a mixed type of reaction. There will be whitish areas, small cysts, and streaks resembling those of leukoplakia. Very rarely the epithelium will be replaced by a thick, red, velvety membrane that in its gross appearance resembles granulation tissue. Under the microscope three types of pathologic picture may be recognized.

Chronic Type. This reveals areas of lymphocytic exudate, rather diffusely scattered through the wall of the pelvis, ureter, or calix. The epithelium may be partially lost and replaced by scars or small ulcers.

Cystic or Follicular Type. As the process continues, the epithelium may form small,

generalized arteriolar sclerosis elsewhere in the body.

In arteriolar nephrosclerosis the kidney may be little or greatly reduced in size, the "shrunken kidney" being common. It is granular and its capsule resists stripping, as it is tacked down to the cortex by innumerable delicate fibrous attachments, which also account for its granularity. The organ is very firm, the cortex is narrowed, its markings are somewhat obscured, and its peripelvic fat is increased in amount.

The microscope reveals generalized fibrosis and scattered collections of lymphocytes in the interstitial tissue where this is thickened. The glomeruli exhibit a variable conversion into fibrous tissue, many of them appearing as fibrous masses of hyaline collagenous tissue. If one examines the hilum of the glomeruli it will be found that the arteriolar loops situated there show thickening of their walls—a thickening that is sometimes so advanced as to compress the lumen into a very small compass or occlude it entirely. There may or may not be hyaline degeneration of the fibrous wall of the arteriole, but it is usually much thicker than normal. The arteries often show sclerosis in varying degrees, but little weight is to be placed upon their appearance in the presence of the more important arteriolar thickening and degeneration.

For the etiology of this condition the reader is referred to textbooks on general pathology or to the excellent and numerous articles on this subject by Goldblatt. Following his discoveries on the importance of renal ischemia by the experimental shutting off of the blood supply to one kidney, it was postulated that this condition favored the elaboration of a substance ("renin") which would act upon a globulin in the serum of the blood known as "hypertensinogen" to produce a pressor substance "hypertensin" or "angiotonin." Later it was believed that renin might be elaborated in the preglomerular bodies described by Oberling and by Goormaghtigh. Recent morphologic investigations by Oberling, however,

indicate that these bodies (also called "juxtaglomerular bodies") are a variety of glomus, rather than glands of internal secretion. They are very variable in normal kidneys, some showing them while others exhibit not a trace of them; they are more constantly observed in the kidneys of some of the lower mammals, like the cat. As far as hypertension is concerned, attempts to find any constant lesion in these preglomerular bodies have thus far been quite fruitless.

Tumors. For discussion of tumors of the kidney see "Tumors of Renal Parenchyma," p. 288.

CALICES, PELVES, AND URETERS

The histology of these portions of the genito-urinary tract is essentially similar, so that their pathologic histology is also necessarily rather uniform. Arising from the hindgut, these structures constitute tubes that extend from the bladder to the innermost portion of the kidneys. They are enclosed in layers of smooth muscle supported by connective tissue and lined by a compound columnar epithelium which the histologists call "transitional" in type, confining that term to this tract alone. (The epithelium of the bladder and upper urethra shares in this type of architecture, but the pathology of these organs will be discussed later.) Inflammation or irritation of the epithelium often leads to metaplasia, usually in the direction of epidermoid changes, whereby the transitional epithelium becomes very much like that of the orificial mucous membranes of the alimentary or other tracts. The muscular coat of the ureters tends to fray out and become less substantial as the calices extend into the kidney; from the pelvis downward its layers are well developed.

Developmental Anomalies. The most frequent anomaly of the ureters is doubling, which may occur unilaterally or bilaterally; in such cases the debouchment of the extra ureter may be ectopic, communicating with the colliculus, vas, or seminal vesicle. There

bacilli clumped on the surface of the epithelium in many instances

Hydronephrosis This condition is the result of any mechanical obstruction of the urinary passages. Among the inherent factors are congenital strictures, scarring as a result of inflammatory processes, and impacted calculi and other such inherent factors, extrinsic factors include pressure on the ureters by tumors, kinking of the ureters as a result of ptosis of the kidneys, or even accidental ligation during pelvic operations. Furthermore, the obstruction may be at some distance down the urinary tract, hypertrophy of the prostate, stricture of the urethra, or other such narrowings in the passageway can bring about a backing up of the urine and distention of the ureters, pelvis, and calices. The process usually increases slowly in its intensity, resulting in atrophy of the muscular coats of the conducting system and finally in a thinning out and atrophy of the renal parenchyma itself, so that the organ may become enormously dilated and cyst like. The parenchyma (what there is of it) is pale and may measure only a few millimeters in thickness. Microscopically there are atrophy and fibrosis, with possibly a certain amount of pyelonephritis of the chronic type. The pathologist is always astonished at the amount of renal tissue that is fairly well preserved in the sections from hydronephrotic kidneys.

Calculus It is probable that most of the stones seen in nephrolithiasis are the result of the deposit of mineral salts in small masses of fibrin or other albuminous substance that accumulates in the course of inflammation. That they may develop *ex vacuo* is possible, but this probably occurs less often than might be supposed. There is evidence that certain chemicals, notably the sulfonamide compounds, may crystallize out in the urine of the collecting tubules and pelvis where the pH is unfavorable for their remaining in solution. Possibly this may happen in the case of other chemicals as

well. Uric acid crystals are seen not infrequently in the papillae of the kidneys of children, these are the "uric acid infarcts." Calculi may form by the exfoliation of epithelium in which there have been deposits of mineral salts. Certain metabolic disturbances, such as those occasioned by parathyroid tumors and deficiencies in vitamins, also contribute to their formation.

The calculi grow by accretion until they may constitute casts of entire pelvis and calices—the so called "staghorn calculi." They may be single or multiple and may lie anywhere in the kidney, sometimes they are tucked away in the depths of a calyx, although usually they are intrapelvic. Arising in the urinary stream, as they do, they are usually composed of combinations of calcium with uric acid, carbonates, or phosphates, or sometimes oxalates of lime. Stones of the last named type are sharp and abrasive and are apt to adhere to the wall of the pelvis or of a calyx or even of the ureter and thus fail to become dislodged and passed. When they do pass they are probably the most painful of the group on account of their abrasive qualities.

The renal tissue abutting on a calculus naturally undergoes marked inflammation of a subacute or chronic variety. Pyelonephritis is common, and infection may produce pyonephrosis in connection with calculus. Thus there is a vicious circle in which inflammation causes calculus and vice versa. Metaplasia of the epithelium of the calices or pelvis is common in connection with calculi, and this usually takes the epidermoid form. In our case of glandular pyelitis a huge staghorn calculus had been present for years. Such metaplasia may be interpreted, of course, as a forerunner of carcinomatous change, and this claim has been made frequently and probably justly. As calculi are passed down the ureter they occasion excruciating pain and may become impacted at the points of normal narrowing—the ureteropelvic junction and the ureteral entrance into the bladder.

thin-walled cysts that apparently represent foci of epithelial downgrowth with subsequent central softening, loss of the cores of the plugs that were thus formed, and production of pseudocysts. These show no true glandular epithelium; rather they resemble Brunn's glands of the bladder. Instead of diffuse lymphocytic exudate, there may be follicular aggregations of these cells in the

The musculature of the pelvic or ureteral wall is not interfered with. Portions of the epithelium may show metaplasia in the more usual direction of epidermoid tissue. With luck one may trace both types from the normal transitional epithelial lining in one section.

The process is manifestly one of anaplasia toward the glandular type of epi-



Pyelitis glandularis. In this rare condition the mucosa of renal pelvis has become transformed into a glandular mucous type resembling that of intestinal tract.

submucosa, which lend to the process a follicular appearance and the name "follicular inflammation."

Glandular Type. This is not uncommonly encountered in the bladder, as we shall see, but it is very rarely observed in the pelvis and ureters. One instance of chronic glandular ureteritis and three of glandular pyelitis have been reported. In this type of inflammation there is complete replacement of the transitional epithelium by the thick, red, velvety membrane referred to above. On microscopic examination this is found to have the appearance of intestinal mucosa, with typical crypts lined with goblet cells that are rather poor imitations of those in the intestine, but good enough to be very surprising when one observes them.

thelium of the embryonal hindgut; with the ureter and pelvis there can be no other very cogent explanation, as urachal rests or other such embryonic structures cannot be brought to bear in the attempt to reconstruct the histogenesis of the lesion. While urachal rests are of importance in the fundus of the bladder, this process may arise anywhere between the bladder and the calices of the kidney. The instances thus far reported have all been connected with chronic pyelonephritis and staghorn calculi.

TUBERCULOUS INFLAMMATION. In this the mucosa of the ureters and pelvis is studded with miliary tubercles which may fuse and undergo caseation, with production of areas of fibrosis and cicatricial contraction as they heal. The microscope will reveal the

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TUMORS OF RENAL PARENCHYMA

EXAMINATION OF URINARY SEDIMENTS
FOR NEOPLASTIC CELLS

Following the promising lead afforded by the success of his method for examining and diagnosing vaginal smears and intra-uterine aspirations, Papanicolaou has lately investigated with Marshall the possibilities of urinary sediments. The work is frankly in its preliminary stages, but it is producing stimulating results. For example, neoplastic cells were recently detected in the urinary sediment from a patient whose bladder showed no tumor and whose pyelograms and renal x-rays were negative. Cystoscopic examination revealed merely a large diverticulum. At operation a vacuum sucker was introduced into this pouch and some rather bulky and granular fragments of neoplastic tissue were aspirated. This proved to be from an epidermoid carcinoma in the diverticulum.

The method consists of the following steps. Approximately 40 cc. of urine is collected (preferably through a catheter) and mixed in a tube with 10 to 20 cc. of 95 per cent alcohol. The urine is then centrifugated at 20,000 r.p.m., and the sediment is smeared on slides that have been filmed with albumen. (It is best to make the smears promptly.) As the next step the preparations are fixed in equal parts of 95 per cent alcohol and ether for ten minutes; they may remain longer in the mixture without harm. They are then stained by Papanicolaou's method* and examined for the presence of neoplastic elements. Naturally, the recognition of these depends upon a sufficient familiarity with tumors of the urinary tract and upon considerable practice.

The method may also be applied to the prostate by obtaining specimens of urine before and after prostatic massage and comparing the smears of their sediments.

* G. N. Papanicolaou, *Science*, 95:2469, 1942.

CLASSIFICATION OF TUMORS

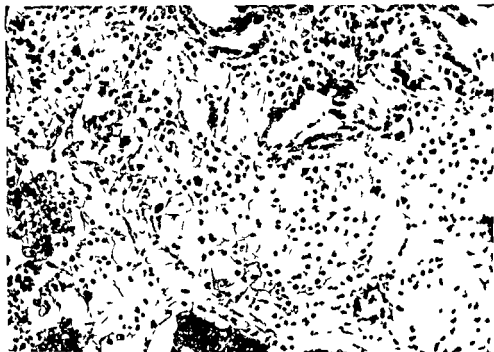
The tumors of the renal parenchyma are described at length by Ewing in his textbook. He divides them into four groups: (1) adenomas; (2) adenocarcinomas and carcinomas arising from renal tubules; (3) papillomas and papillary carcinomas of the renal pelvis; and (4) adrenal tumors. This is a simple classification, but it must be subdivided and modified to a slight extent. The subdivisions have already been made by Ewing in his book, but his arrangement of the sequence of subject matter is somewhat confusing to the inexperienced reader who is seeking enlightenment. His differentiation of embryonal malignant tumors of childhood from those of later life is probably justified, but it is not calculated to clarify the subject. His "adrenal tumors" are coming more and more to be considered as of actual renal origin.

Adenoma. Renal adenomas may be congenital, arising from isolated foci of renal tubules, or they may be the result of sclerotic changes in the organ, developing in cysts that follow nephrosclerosis. They may be single or multiple. Usually they attain only trifling dimensions, seldom over a centimeter in diameter, although occasional very large examples may be reported. As often as not they are discovered quite accidentally at operation or necropsy. Ewing recognized three microscopic types: papillary cyst-adenoma, alveolar adenoma, and tubular adenoma. These are all composed of rather compact granular cells that may show changes similar to those observed in degenerating renal epithelium. As their names are quite descriptive it is scarcely worth while to dilate upon them.

Adenocarcinoma. EMBRYONAL GROUP. *Adenocarcinoma of Infants.* This is sometimes known as "renal embryoma." Very little insight as to its nature can be gained from gross examination. It is rare except in children's hospitals where surgery is highly developed. Microscopically the pathologist is at once struck by the immaturity

of the tumor's type-cells and their unusual arrangement, which is sometimes so lawless and atypical that it suggests that of a sarcoma. This tumor may be essentially similar to the Wilms' tumor, but it represents a concentration on epithelial development, rather than a mixture of epithelial and connective tissue or muscular growth. The cells are arranged in alveoli or tubules and some-

Embryonal Adenomyosarcoma This mixed tumor is usually called "Wilms' tumor," although the longer name avoids eponymic nomenclature and describes its nature by implication. It is a tumor of infancy, rarely seen after the tenth year, as it develops and runs a fatal course within the first few years of life. It may occasionally be observed in elderly adults, possibly as a result



Embryonal carcinoma of kidney, from adult patient. There are two types of cell: one is small and hyperchromatic, the other pale and more or less squamous. There is no typical picture for this versatile tumor.

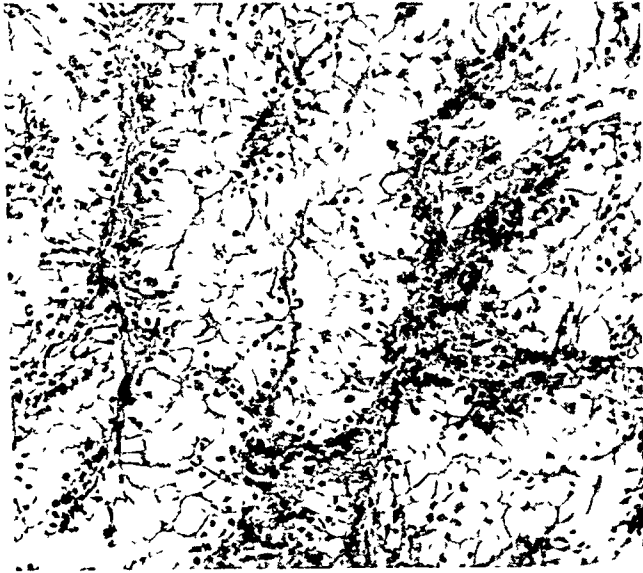
times exhibit structures that suggest glomeruli of the mesonephros.

Embryonal Carcinoma of Adults This tumor occasionally turns up in general surgical practice, it is large and soft and rather well outlined, and it may develop at any point in the renal parenchyma. Microscopically it closely resembles the testicular embryonal carcinoma, as it is composed of anastomotic cords or tubules that are pale and vesicular and possess vesicular nuclei. When such tumors also exhibit glomeruloid structures they are not very dissimilar from the infantile adenocarcinoma. Ewing spoke of them as "tumors of the renal blastema," which would imply that they were "mesonephromas."

of latency attributable to occasionally better differentiation with less inherent malignancy. It is generally subcapsular and may arise at any point and grow to considerable size (15 to 20 cm. or more). It may also appear to lie entirely outside of the kidney. Such tumors have been reported as weighing 3,500 Gm. The neoplasm may be solid and opaque, but as it grows it can become cystic; it is not usually hemorrhagic until late in its existence, when it begins to break down. It rarely metastasizes, but its size and situation together with the toxemia that develops along with it bring on a fatal outcome.

The microscopic structure of this growth is that of a decidedly mixed tumor, like the

embryoma it may show tubules, cysts, and papillary areas, together with alveolar grouping and abortive glomerular structures; but unlike that neoplasm it also exhibits definitely sarcomatous elements—not only fusiform cells, but recognizable myoblasts of the smooth or striated variety, cartilage and bone. It apparently arises in mesodermal tissue from the mesonephros, possibly that portion known as the “meso-



Typical “hypernephroma” (solid clear-celled carcinoma) of kidney. Note that large, clear cells do not form any tubular or papillary structures.

blastema.” There are some tumors that are predominantly muscular or fibrous, and many of these appear like simple lipomas, fibromas, and the like. Liposarcomas may develop in the perirenal fat and should not be confused with them.

ADULT FORMS OF MALIGNANT TUMORS. PAPILLARY ADENOCARCINOMA. This is the most common malignant tumor of the kidney; it comprises three subtypes that Ewing recognized microscopically.

Clear-celled Carcinoma (Renal-celled Carcinoma). This is a bulky and very hemorrhagic growth. It is situated in a pole or near the pelvis of the kidney; and it is of a yellowish-orange color, though it may be white. Grossly it cannot be differentiated by its site or by its appearance from the so-called “hypernephroma.” Microscopi-

cally it is composed of large clear cells with nuclei that vary in size and in density; they often seem too well differentiated to be malignant. They are arranged in alveoli or tubules, or sometimes they are around the periphery of cystic spaces, into which they project as pseudopapillae. Occasionally there are areas where the cells are smaller, denser, more granular, and more opaque, approaching those of the granular-celled papillary carcinoma (see below) in their appearance. These clear-celled tumors often metastasize to the lungs and skeleton, but metastasis may be late and single, so that primary and metastatic tumors may be removed with a fair chance that the growth has been eradicated. This is very seldom true of other malignant tumors. The type-cell is clear because it contains much fluid in which fats, lipids, and glycogen may be



“Hypernephroma” metastasizing to bone, where it is destroying the trabeculae. In this figure these appear as grayish structures, some of them slightly out of focus.

demonstrated by the use of appropriate methods of staining.

Papillary Carcinoma with Granular Cells. This may occur in sclerotic kidneys, as do the adenomas, or it may arise in practically normal organs. It may be single or multiple, tending to be larger when single. It is whitish and fairly well defined, and it does not tend to cause much hemorrhage. Sometimes its cells, which are typically rather opaque, compact, and granular, may show small



Papillary cystadenocarcinoma of kidney with granular cells (Compare with example of clear celled type)

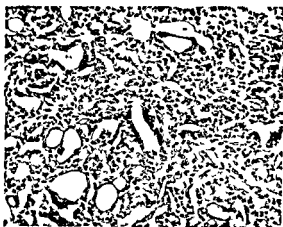
amounts of fatty infiltration, but they are not universally vesicular. The tumor tends to grow in a papillary fashion from the walls of cyst like cavities which it more or less completely fills.

Malignant Adenoma Ewing recognized an "adenoma malignum" that develops from the cystadenomas of the renal parenchyma. It is not evident why this distinction should be made.

TUBULAR ADENOCARCINOMA This originates in cortical tubules or in the renal blastema and may be situated in any part of the kidney, or (should it have mesonephric origin) it may lie outside of the kidney like some forms of the Wilms' tumor. It attains considerable size, and although it may remain for a long time encapsulated it ultimately becomes infiltrating and metastasizes widely. Microscopically a solid or tubular type of growth is observable, with a fairly close resemblance to renal parenchyma, the cells vary from cuboidal to columnar. At times it is difficult to decide whether some of the tubules in such a tumor belong to it or represent metaplastic tubules native to the kidney that have been stimu-

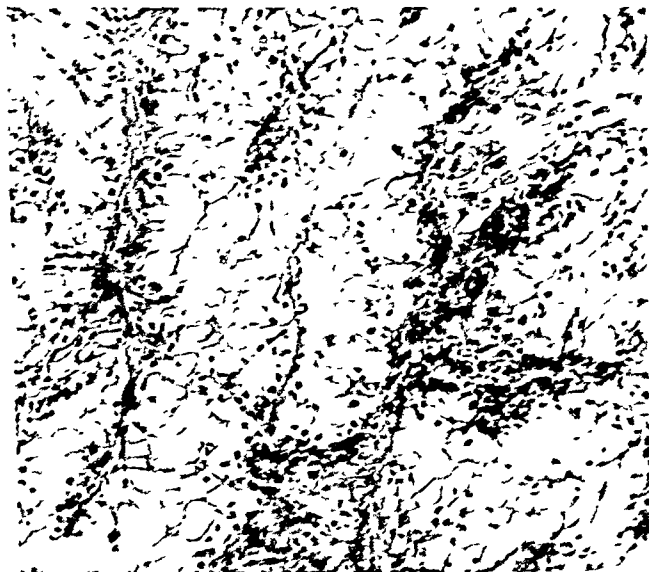
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"HYPERNEPHROMA" This was first described by von Grütz as originating from rests of suprarenal tissue in the kidney, and his theory was promptly accepted and has gone almost unchallenged for years. Stoerck,



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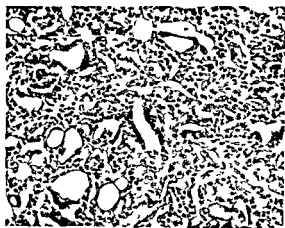
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however, disputed this idea and attempted to demonstrate that the tumor derived from altered renal epithelium in adenomatous areas. It cannot be denied (particularly after personal observation) that the suprarenal and renal tissue may become intermingled along the apposed surfaces of the two organs. During embryonal development the suprarenal tissue grows more rapidly



Large hypernephroid tumor which is usurping greater part of medulla of this kidney. The tumor is orange-yellow mottled with bright red hemorrhagic areas. (Army Medical Museum 65596.)

than does the kidney and almost encircles it. Moreover, there are aberrant suprarenal rests to be found along the suprarenal vein and solar plexus and over the inferior surface of the liver; they may also be observed along the course of the spermatic vein and cord, or in the broad ligament, or about the uterus, tubes, or ovaries. The intra-ovarian rests may develop into tumors that produce marked virilization in women who exhibit them. Virilization is also characteristic of tumors of the suprarenal cortex proper.

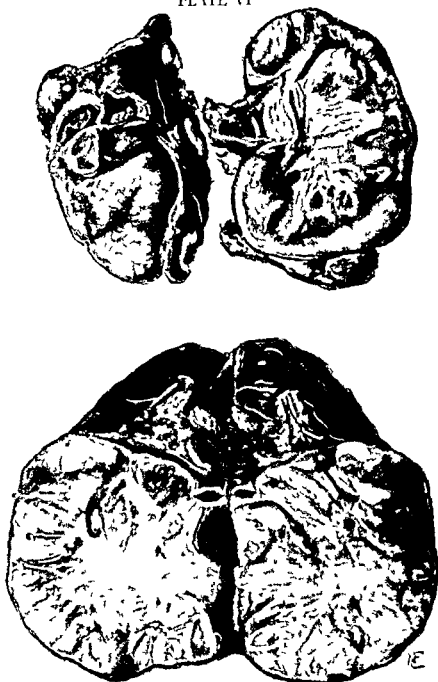
The renal "hypernephroma" has the same gross characteristics as those of the clear-celled papillary adenocarcinoma, and its microscopic appearance is the same in all respects save one: it exhibits solid masses of cells enclosed in a delicate stroma that do not form tubules, cysts, or papillae. This

seems to be the only distinguishing feature. Search of a clear-celled carcinoma will shortly reveal considerable areas in the section where no lumina can be demonstrated. Tumors of undisputedly suprarenal cortical origin exhibit characteristic symptoms that have just been enumerated; the "hypernephroma" shows none of them.

In such authoritative textbooks as those of Ewing, Karsner, and Boyd it will be found that the first goes into an elaborate explanation of the distinguishing differences between hypernephroma and clear-celled carcinoma based on these microscopic characteristics, the second describes them rather briefly, and the third expresses an inclination to combine them both under the term "hypernephroma," as this is sanctified by long usage. Boyd makes it plain, however, that he considers both growths to be of renal origin. There seems to be little reason, then, to retain the misleading name "hypernephroma" and to maintain two separate categories for these two essentially identical neoplasms. As a concession to usage the term "hypernephroid tumor" is sometimes employed; this is harmless and noncommittal.

Tumors of Renal Pelvis. PAPILLOMA. A simple papilloma of the transitional type of epithelium is a not uncommon finding in the renal pelvis, and it is the same tumor that may develop anywhere between the tip of a calyx and the prostatic urethra. It forms a villous patch on the smooth mucosa, with its papillae suspended and waving like the tentacles of a sea anemone in the urinary contents of the pelvis. Under the microscope it is found to be composed of true papillae of delicate and vascular stroma, with pseudopapillae extending out from some of them. The epithelium is of the compound columnar, sometimes fusiform, type that is typically transitional. These tumors may be single or multiple. Owing to the delicacy of their villi, these are readily broken off, and copious hemorrhage may ensue from the severed vessels of the stroma.

PLATE VI



(Top) Tuberculous kidney, bisected so as to demonstrate external appearance of one half and sectioned surface of the other. Note large cyst containing remnants of chalky, caseous material that was evacuated from it. Below this are tubercles, represented by pale raised areas. There is a zone of yellowish brown necrotic material about the calices in interior of organ (right hand picture).

(Bottom) Typical clear celled carcinoma in lower pole of kidney. In gross it cannot be distinguished from hypernephroma and probably should not be (see text).

however, disputed this idea and attempted to demonstrate that the tumor derived from altered renal epithelium in adenomatous areas. It cannot be denied (particularly after personal observation) that the suprarenal and renal tissue may become intermingled along the apposed surfaces of the two organs. During embryonal development the suprarenal tissue grows more rapidly



Large hypernephroid tumor which is usurping greater part of medulla of this kidney. The tumor is orange-yellow mottled with bright red hemorrhagic areas (Army Medical Museum 65596.)

than does the kidney and almost encircles it. Moreover, there are aberrant suprarenal rests to be found along the suprarenal vein and solar plexus and over the inferior surface of the liver; they may also be observed along the course of the spermatic vein and cord, or in the broad ligament, or about the uterus, tubes, or ovaries. The intra-ovarian rests may develop into tumors that produce marked virilization in women who exhibit them. Virilization is also characteristic of tumors of the suprarenal cortex proper.

The renal "hypernephroma" has the same gross characteristics as those of the clear-celled papillary adenocarcinoma, and its microscopic appearance is the same in all respects save one: it exhibits solid masses of cells enclosed in a delicate stroma that do not form tubules, cysts, or papillae. This

seems to be the only distinguishing feature. Search of a clear-celled carcinoma will shortly reveal considerable areas in the section where no lumina can be demonstrated. Tumors of undisputedly suprarenal cortical origin exhibit characteristic symptoms that have just been enumerated; the "hypernephroma" shows none of them.

In such authoritative textbooks as those of Ewing, Karsner, and Boyd it will be found that the first goes into an elaborate explanation of the distinguishing differences between hypernephroma and clear-celled carcinoma based on these microscopic characteristics, the second describes them rather briefly, and the third expresses an inclination to combine them both under the term "hypernephroma," as this is sanctified by long usage. Boyd makes it plain, however, that he considers both growths to be of renal origin. There seems to be little reason, then, to retain the misleading name "hypernephroma" and to maintain two separate categories for these two essentially identical neoplasms. As a concession to usage the term "hypernephroid tumor" is sometimes employed; this is harmless and noncommittal.

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TRANSITIONAL CELLED CARCINOMA This is also common to the entire conducting apparatus of the urinary tract and the bladder. It may develop deep in the kidney, where it may arise from the tip of a calyx and appear somewhat similar to the papilloma except that it is more solid and less feathery, tending also to be more sessile. Microscopically it reveals a structure that varies from a slightly malignant looking papilloma, not very well differentiated and exhibiting many mitotic figures, to a rather solid mass of poorly differentiated transitional cells that have become large and polyhedral. These grow in many layers and show numerous mitoses. Sometimes the metaplasia takes the form of a tendency to imitate epidermoid epithelium. Such tumors may infiltrate the parenchyma beneath them, and they metastasize widely.

EPIDERMOID CARCINOMA (SQUAMOUS-CELLED CARCINOMA) In this tumor there is a frank departure from the papillary to the flat and skin like type of growth that thickens the pelvic epithelium in the form of a hard, almost horny patch. It may arise in the ureter as well as in the pelvis. Under microscopic examination it does not differ from any other epidermoid carcinoma, it forms pearls of whorled and keratinized squamous cells and invades the underlying tissue. It metastasizes like its relatives in other parts of the body. That it is an outcome of metaplasia attributable to irritation by calculi (leukoplakia) is often claimed and probably true.

ALVEOLAR CARCINOMA Ewing describes an alveolar carcinoma of the renal pelvis which, he adds, is not very different from the papillary or epidermoid variety. In this tumor one may see the typical alveolar arrangement of cells that are large and ovoid, or these may penetrate the pyramids of the kidney and infiltrate them in the form of interlacing cords that provoke a desmoplastic reaction. It is a rare tumor, we have received only two in the course of ten years or more.

Perirenal Tumors The renal hilus may be the site of nonmalignant and malignant mucoid, fibrous, or fatty tumors, sarcomas derived from these are occasionally observed, liposarcomas are commoner. Lymphosarcoma may develop in the kidney, as may focal leucosarcoma in myelogenous or lymphogenous leukemia. Neurilemmoma may arise from the nerves in the vicinity of the organ and form a large yellow growth that may weigh 50 Gm or more and so closely resemble a hard liposarcoma that it may be mistaken for one very readily. The largest simple neurilemmoma in our collection was of perirenal origin. The kidneys may also be the site of metastases from malignant primary tumors of other organs particularly the lungs.

Treatment and Prognosis The only renal tumors holding out much encouragement to treatment by x irradiation are the adenomyosarcomas (Wilms') and embryonal carcinomas. The former are very much like lymphosarcomas in their reaction to irradiation, disappearing under the treatment and raising the hopes of all concerned, only to recur within a matter of months. With each recurrence (again like the lymphosarcomas) they appear to acquire increased radioresistance. This leaves surgery the paramount procedure in connection with renal tumors. The prognosis depends upon the thoroughness of the removal of the tumors and of their metastases. As they are usually well contained within the kidney a nephrectomy will remove the entire growth, and if it has not metastasized the prognosis will be good.

URINARY BLADDER

Congenital Anomalies The most frequent congenital anomaly of the bladder is extrophy, a wide gaping of the anterior wall of the organ on account of the failure of union of the lateral portions of the urogenital cleft. The bladder constitutes a red pouch that opens without any formality upon the outer world. With this may go failure of union of the pelvic bones at the

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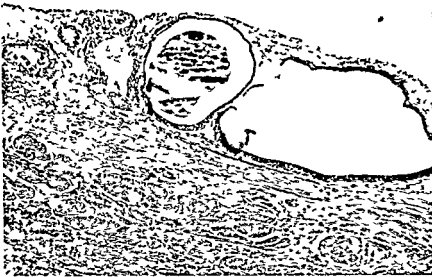
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Inflammation **CHRONIC CYSTITIS** The acute inflammations of the bladder do not concern us, but the chronic forms that may follow them or may begin as chronic inflammation may give rise to lesions that will require diagnostic biopsy. The mucosa becomes thickened and may show ulcerations, and it is accompanied by thickening



Cystitis cystica. Larger and smaller pseudocysts lie within inflamed transitional mucosa. There is no true glandular epithelium present.

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symphysis. The vesical mucosa undergoes extensive glandular metaplasia; in fact this is the commonest cause for the formation of this atopic epithelium. On the other hand, the urachus or portions thereof may remain patent and form a canal leading off the bladder toward the umbilicus. This duct is usually lined with glandular epithelium of a mucous type, and from it tumors may



Photomicrograph of intestinal crypts taken not from intestine but from mucosa of an exstrophic bladder. Is this metaplasia, or is it faulty differentiation (or lack thereof) from cloacal mucosa?

develop. Under certain circumstances it may become extensively and acutely inflamed.

Calculi and Foreign Bodies. After disease of the vesical mucosa, calculi are apt to form in the retained urine, or they may build up by accretion about nuclei of protein material. They vary in diameter from a few millimeters to several centimeters. Stones may form without any apparent inflammatory stimulus in conditions where there is oversecretion of uric acid or urates, or they may form about oxalate calculi that have come down from the kidney. Calcareous calculi may be produced by accretions of calcium salts about one of these smaller stones. Sometimes so many tiny calculi are present that they are spoken of as "gravel."

The introduction of foreign bodies from without, through the urethra, may be in etiologic factor. Catheters have been known to break off in the bladder, or various crude instruments may be introduced by the patient and lost into the bladder. Among these wax bougies, fruiting stalks of grass, knitting needles, and hairpins have been found



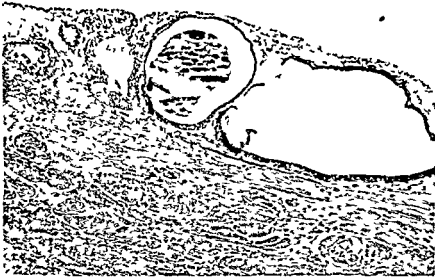
Section of vesical mucosa from a case of exstrophy of bladder. Note that it bears no resemblance to normal transitional vesical epithelium, while it strongly resembles that of intestinal tract.

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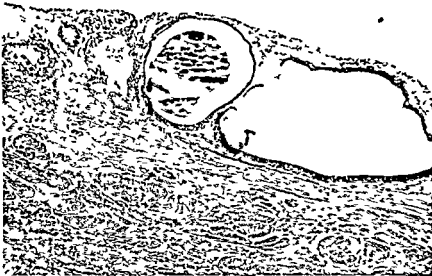
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Biopsy from bladder of woman who complained merely of passing "milky urine." There has been complete metamorphosis of normal transitional epithelium into epidermoid epithelium, with a heavy keratinized layer scaling off into urine. This "dandruff" caused the milkiness.

squamous instead of transitional epithelium.

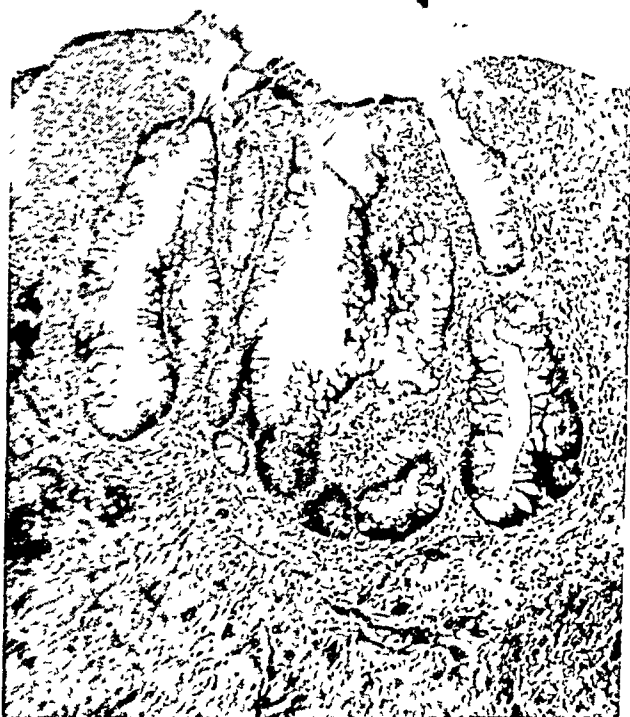
One extraordinary instance of metaplasia was observed in our hospital. It produced a large patch several centimeters in diameter in the posterior vesical wall. This was so cornified that an instrument would grate upon it. Microscopically there was a heavy keratinized layer that was desquamating briskly, and under it a thick stratum granulosum. Beneath this were typical prickly cells with intercellular bridges. Here and there the epithelium was thrown up into heavily keratinized papillomas or warts. The patient merely complained of passing foul, turbid, and milky urine. This contained desquamated cornified cells like those of a sebaceous cyst.

Another form of metaplasia is directed toward the formation of glandular epithelium, as already described in connection with the renal pelvis. This is not uncommon in the bladder, particularly in connection with exstrophy.

These forms of metaplasia probably have a definite bearing upon the development of epidermoid and glandular carcinomas of the bladder; one need not search for embryonal rests to explain them except when they

occur near the site of the urachus in the fundus.

HUNNER'S ULCER. There is a very sluggish form of ulcer that may be found on the vesical mucosa of middle-aged women, rather than in men. It occurs in connection



Cystitis glandularis. Typical mucous glands with goblet cells found in neighborhood of trigone near a carcinoma of bladder.

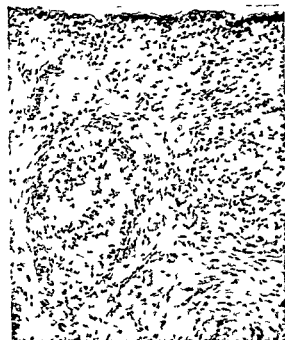
with diffuse cystitis. Its microscopic picture is most undramatic, revealing merely a very sluggish, sloughing ulcer with remarkably little cellular reaction about it.

MALAKOPLAKIA Little is understood concerning this lesion, which usually occurs in

middle aged women but may be observed on occasion in men and children. The mucosa is studded with rounded, firm plaques surrounded by hyperemic zones. Microscopically these prove to be collections of phagocytes underlying patches of thickened mucosa which is ulcerated only at the center of the patch. The phagocytes contain odds and ends of nuclear material, erythrocytes, and bacteria which they have



Early metaplasia in cystitis glandularis. mucous cells at left developing from normal transitional epithelium at right



Section from crater of Hunner's in dolent ulcer of bladder. There is no mucosa; the entire tissue is composed of collagenous material in which there are two edematous lymphoid structures.



Section through wall of a diverticulum of bladder. Muscle is much thinned out, as most of it is included in this microscopic field.

taken up. Michaelis Gutmann bodies, which somewhat resemble Russell bodies, may be found in the cells of the plaques or lying free among them. These bodies present a concentric lamination and may contain iron and calcium salts.

INFECTIOUS GRANULOMA Tuberculosis
In men this usually develops in the trigone about the mouths of the ureters, hence the inference is that the mode of infection is downward from the ureters rather than upward from the prostate or seminal vesicles; furthermore, it has the same distribution in the female. Tubercles arise at this point, break down, and spread along the mucosa, giving rise to ulcers with raised whitish edges that may show daughter tubercles which have not as yet broken down. The ulcers are surrounded by zones

of hyperemia. Sometimes they occasion polypoid proliferation of the mucosa which may be mistaken for papilloma. Microscopically they show the characteristics of tuberculous lesions in general.

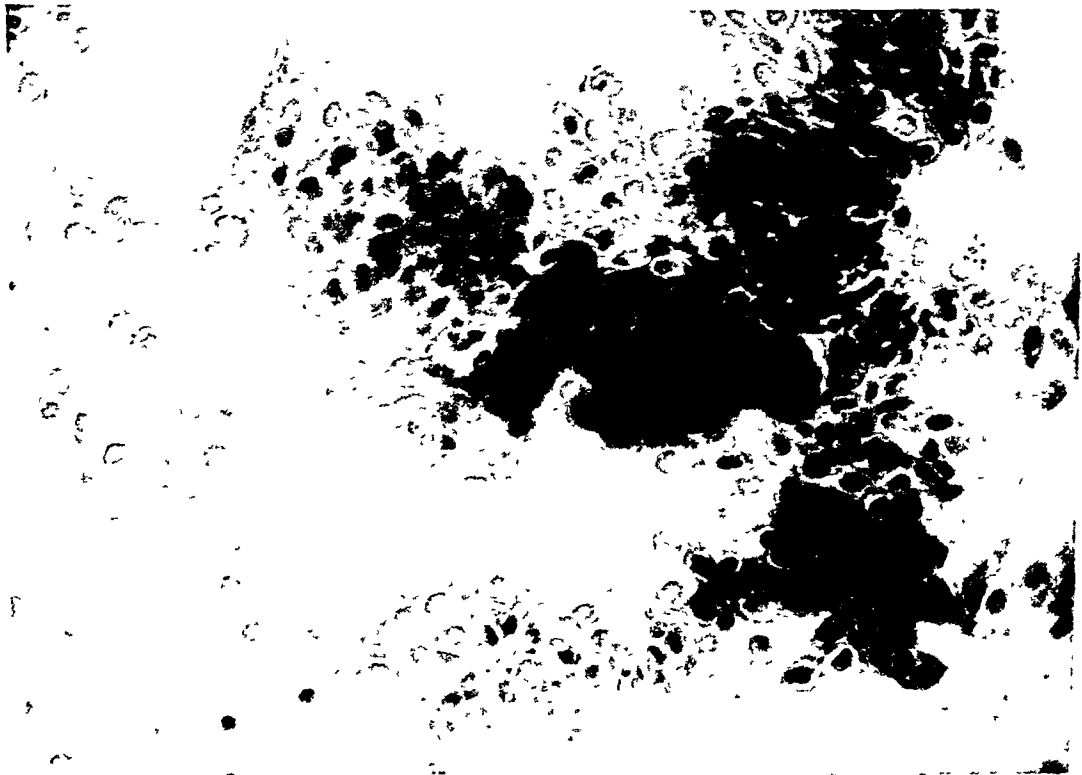


Massive but well-differentiated transitional papilloma of bladder. Cells are feathery, not heaped up, and do not infiltrate the stroma. They show no evidence of rapid growth in the form of mitotic figures.

Syphilis. Although it is not common in the bladder, lues may produce mucous patches in that situation, and gummata may rarely develop in the region of the trigone.

Diverticula. Owing to obstruction, usually from urethral stricture or enlarged prostate, the bladder not only becomes trabeculated, but the wall bulges out into the meshes of the trabecular network, forming capacious diverticular pouches. These may become infected, stones may form in them, and, in some cases, malignant tumors may arise about their orifices. Less frequently "true diverticula" may be observed as congenital anomalies, usually in the vicinity of the vestigial urachus or the trigone.

Tumors. PAPILLOMA. The commonest tumor of the bladder is the transitional-celled papilloma. This is an overgrowth of the lining epithelium that takes the form of a patch of villous projections that float in the urine like clusters of seaweed. They are in no way different from those observed in the renal pelvis and ureter (q.v.), and their apparently innocent histologic appear-



Photomicrograph of smear of crushed fragments of low-grade transitional carcinoma of bladder obtained in irrigating fluid, fixed with heat, and stained with hematoxylin-eosin. This shows the possibilities for diagnosis without benefit of frozen sections.



Typical papillary transitional carcinoma of urinary bladder, cellular differentiation is fair and mitoses few. Tumor is not very malignant

ance is considerably overbalanced by their tendency to be very vascular and fragile, hence extremely hemorrhagic. They may be small and either pedunculated or sessile, and they may attain several centimeters in diameter. When surgically removed all resemblance to water plants is lost, and the tumor is an unlovely mass like wet wool. It may exhibit extensive necrosis of a superficial type.

EPIDERMOID PAPILLOMA Very occasionally small, hard tumors resembling small orange seeds in clusters may be observed on the vesical mucosa. Microscopic examination of these proves them to be composed of epidermoid epithelium, with considerable keratinization of their superficial cells and more or less acanthosis beneath this. There is no reason to consider them in any way dangerous.

CARCINOMA Carcinomas are usually of the transitional type; grossly they are bulkier than the papillomas, although if they are of the less malignant variety they may be distinctly papillomatous in their architecture. They exhibit several types

which are distinguishable mainly by their microscopic characteristics.

Transitional celled Carcinoma These comprise many layers of more or less well differentiated transitional cells tending to



Well differentiated "low grade" transitional carcinoma of bladder. Cells are too numerous and there are mitotic figures that indicate the growth's malignant nature.

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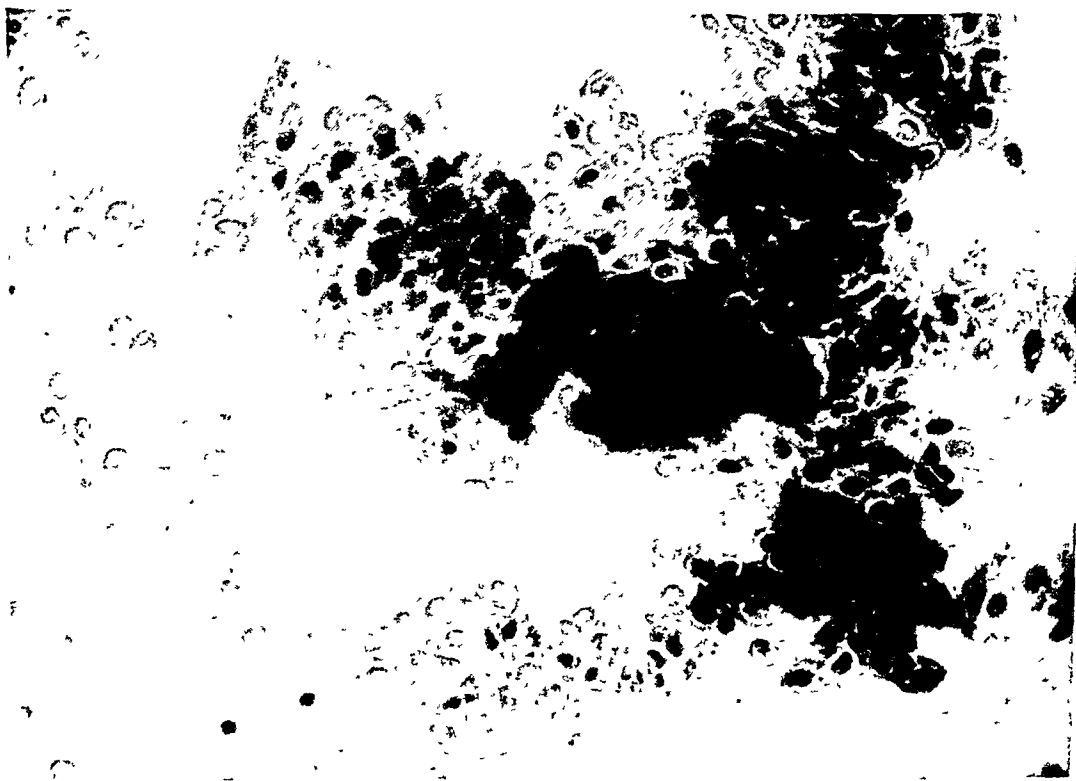


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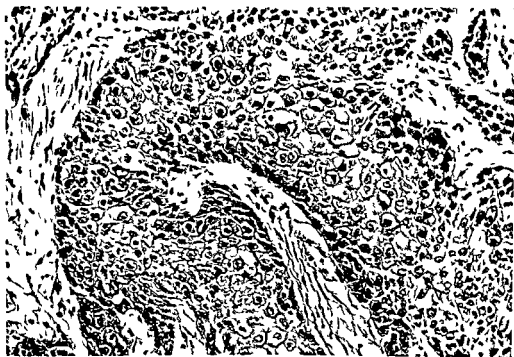
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Although they may begin in papillary forms of neoplasm, they become more malignant as they develop

Epidermoid Carcinoma This is not the keratinizing form that Ewing called by this name, but a genuine epidermoid tumor that is very occasionally found on the mucosa of the bladder in the shape of a hard, flat,

the use of x rays and radium for these carcinomas, which are not radiosensitive

ADENOMA A true adenoma of the bladder is rarely seen, but it has been described. These tumors are likely to be situated in the vicinity of the vestigial urachus, from which they are supposed to develop, the possibility of their deriving from glandular meta



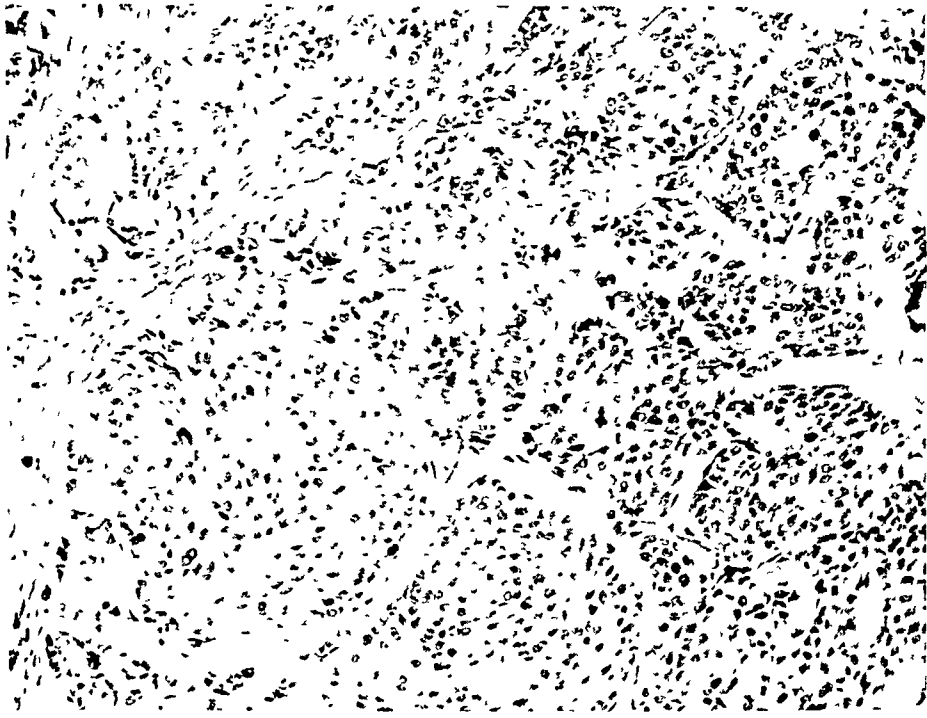
Epidermoid carcinoma of urinary bladder. Its cells are large and squamous and variably keratinized.

and rather plate like growth. It is gray and somewhat translucent, and it tends to curl back upon itself, presenting a convex surface when it is removed from its site. The growth infiltrates the vesical wall and has all the microscopic characteristics of an epidermoid carcinoma.

Treatment of Carcinomas of Bladder Stewart takes a rather pessimistic view of the results obtained by roentgenotherapy in carcinoma of the bladder. It was formerly employed by some of the surgeons in our hospital, as were radon seed implantations, but of late there has been a return to simple surgical eradication which indicates a certain amount of dissatisfaction on the part of urologists with the results obtained by

plasia of the vesical epithelium is always present. They may be fairly large, soft, smooth growths that do not suggest papilloma. Microscopically they are somewhat similar to polypoid adenomas of the alimentary tract. They should not be confused with pseudo adenomatous growth in transitional tumors that have softened and undergone cystic degeneration.

ADENOCARCINOMA This tumor is more frequently seen than the adenoma. It represents either a pseudo adenomatous growth like those just mentioned, in which there is malignant degeneration, or it may be a true adenocarcinoma with cells that resemble those of the intestinal mucosa. Again, when this tumor is in the fundus the presumption



Metaplastic and alveolar form of transitional-celled carcinoma of urinary bladder. It is very invasive in this instance.

grow from a stroma that has a roughly papillary architecture. Mitotic figures may be numerous. As the process increases in virulence the cells exhibit less differentiation, becoming polygonal and being arranged in bulky masses of many layers. They invade the underlying vesical musculature. Very pleomorphic varieties may sometimes be noted. This is the commonest type of vesical carcinoma.

Keratinizing Carcinoma. There are examples that exhibit little orderly arrangement and the cells of which are more or less keratinized in places. It appears as though the transitional epithelium were becoming more epidermoid, but true epidermoid structure is not seen. Ewing called these "epidermoid carcinomas." They are more malignant than the transitional type.

Diffuse Carcinoma. This is entirely dissociated and its cells are so widely scattered and so resemble lymphocytes that it might be mistaken for a lymphosarcoma. It invades the wall deeply and metastasizes widely to the lungs and to bone, where it may take on a more organized form of growth. Its cells have hyperchromatic nuclei that overshadow the scanty cytoplasm.

Aniline Tumors. The aniline tumors of the bladder, apparently caused by long exposure to alpha- and betanaphthylamin and benzidine, develop into rather characteristically keratinized or solid types that occupy a position midway between a metaplastic transitional-celled and an epidermoid carcinoma. They infiltrate the vesical wall rather deeply and diffusely, forming nests of neoplastic cells beneath the mucosa.

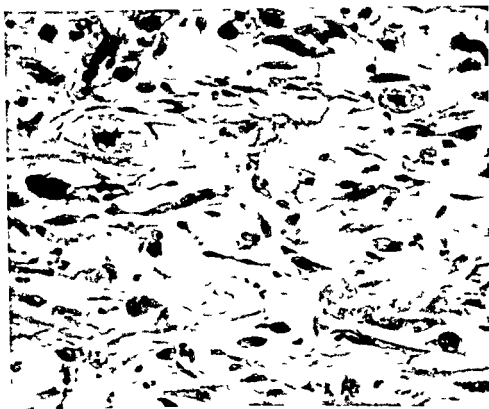


Very marked metaplasia in infiltrating carcinoma of urinary bladder. Ewing called this type "epidermoid carcinoma."

rhabdomyoblasts. With these there are the usual gourd shaped giant cells with the characteristic vacuoles and lines of beaded fibrils within their cytoplasm. The origin of rhabdomyomas and their malignant analogue in the bladder is probably to be explained on a basis similar to that which is adduced for the origin of uterine rhabdo-

myomas where along either the dorsum of the penis (epispadias) or the under surface of that organ (hypospadias). Both of these conditions are usually associated with other malformations, underdevelopment of the penis, exstrophy of the bladder, and the like.

A very distressing anomaly may cause urinary retention in young boys. It is so



High powered view of rhabdomyosarcoma of female urethra which also involved the bladder. Note extremely bizarre cells and two abnormal mitotic divisions.

myomas rests of striated muscle that are displaced into the genito urinary tract during embryonal development.

URETHRA

(The prostate, although intimately associated with the urinary tract, will be discussed under the male genital system.)

Congenital Anomalies. As the urethra of the male is far longer and more complex than that of the female, it naturally presents more opportunity for accidents in development. During its formation this canal may become diverted and emerge some-

where along either the dorsum of the penis (epispadias) or the under surface of that organ (hypospadias). Both of these conditions are usually associated with other malformations, underdevelopment of the penis, exstrophy of the bladder, and the like.

A very distressing anomaly may cause urinary retention in young boys. It is so

slight and trivial that its results are out of all proportion to the damage it may occasion. On occasion the distended bladder has been mistaken for a cyst and the patient has died from peritonitis after operation. The deformity consists in a bicuspid valve near the verumontanum from which two gossamer thin membranes run upward or downward and form sacs that permit the ready passage of a catheter but partially or completely obstruct the normal passage and interfere with the evacuation of the bladder. There may be but one leaflet, or the deformity may take the form of a diaphragm



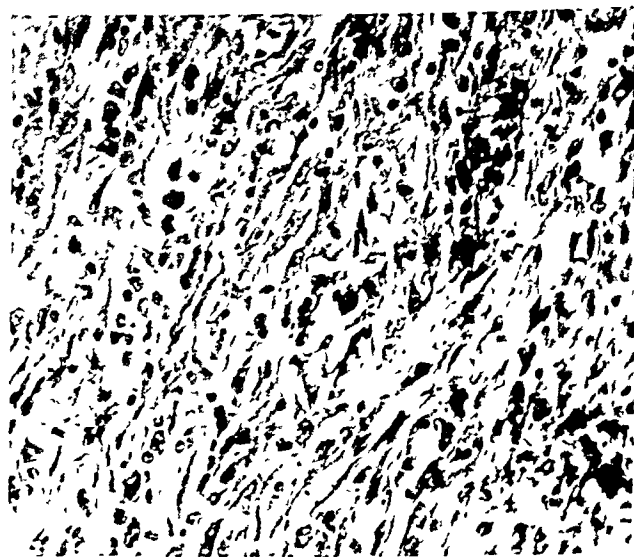
True adenocarcinoma of urinary bladder developing from long-standing cystitis glandularis near the trigone. (Not to be confused with adenocarcinoma of urachal origin.)

is that it develops from urachal rests; when it lies near the neck of the bladder it may and sometimes does represent carcinomatous growth from an area of glandular metaplasia. Such areas may be observed at the margins of adenocarcinomas.

SECONDARY TUMORS. The bladder may be invaded by neoplasms growing in adjacent organs like the rectum or the uterus or prostate; one must guard against diagnosing a primary adenocarcinoma of the bladder unless all such invasion has been strictly ruled out.

OTHER VESICAL TUMORS. It might be expected that in the bladder, which is so largely composed of smooth muscle, leiomyoma would be a common tumor, but although it is found in the neighboring prostate it is relatively rare in the urinary bladder. When found it projects as a large, polypoid tumor covered by vesical mucosa and presenting the usual microscopic features of a leiomyoma. Fibromas and myxomas, too, are uncommon, although myxosarcoma has been reported, as has been rhabdomyoma. Occasionally one encounters metaplastic muscular tumors that most

closely resemble leiomyosarcomas. Rhabdomyosarcoma, which is more common in the prostate, may grow very widely in the urinary bladder, involving almost the entire wall in an infiltrating growth of the typically grotesque fusiform or strap-like

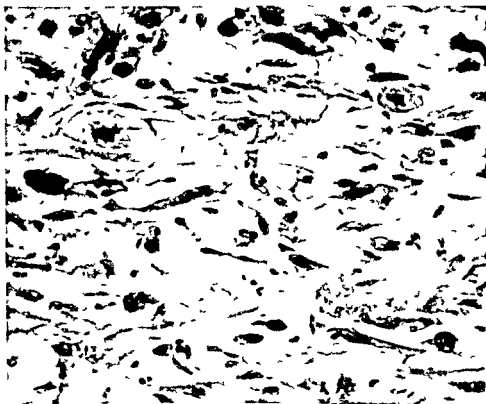


Section of bulky, meat-brown tumor of vesical wall that grew beneath epithelium and involved much of the bladder. It was a leiomyosarcoma so far as this field is concerned, though elsewhere it occasionally exhibited groups of striated cells.

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with a small central orifice. Congenital strictures may be observed in the penile urethra, or there may be atresia with complete lack of canalization.

Inflammation. The various types of urethritis are seldom surgical problems, and the strictures that they leave behind them, while surgically treated, produce no diagnostic problems for the surgical pathologist. Specific granulomata may be found in the urethra but are of little surgical importance except in so far as they occasion dilatation of the bladder, ureters, or renal pelvis.

Urethral Caruncle. This is observed in the case of elderly women and may take one of two forms: it may be granulomatous and belong to the category of chronic inflammations, or it may be adenomatous and constitute a small adenoma, in which case it is a neoplasm. The granulomatous type is a loosely knit mass of almost telangiectatic granulation tissue containing many leukocytes of the type that usually respond to chronic inflammation. The epithelial type may be adenomatous or it may take a papillomatous form and resemble an exaggerated leukoplakia or verruca.

Tumors. CARCINOMA. The usual type of carcinoma in the urethra is epidermoid, although adenocarcinomas may occasionally arise in the glands that empty into this canal. Carcinomas are relatively rare, only one or two having been noted on our service in the past decade.

RHABDOMYOSARCOMA. This is probably a very rare urethral growth, but one has been recently removed from the external orifice of the urethra of a woman in our hospital. The tumor constitutes a semipedunculated, firm, elastic growth that springs from the wall of the urethra and, in the case mentioned, protruded like a polyp. Microscopically it resembles the rhabdomyosarcoma of the urinary bladder in every respect and may occur in conjunction therewith.

PENIS

Although this organ serves the male urinary and reproductive systems conjointly

(the excretory and secretory ducts of both merge near its base in the penile urethra), it seems more logical to discuss it as part of the urinary tract, since it is employed far more frequently to empty the urinary bladder than it is for the purpose of reproduction.

Congenital Anomalies. There are a number of these, such as complete aplasia, congenital over- or underdevelopment, abnormal exit of the urethra in epi- and hypospadias, and other less important anomalies. The prepuce may present several of these, but with the exception of phimosis they are of little importance in surgical pathology.

PHIMOSIS. This may be congenital (a boy being born with a long, tight foreskin which cannot be retracted) or it may result from inflammatory contractions and scars consequent to various types of balanoposthitis occasioning constriction of the preputial orifice or adhesions between the prepuce and the glans penis which prevent its retraction. The corollary of phimosis is paraphimosis, in which the prepuce (once it has been forcibly retracted) cannot be brought down again over the glans. In such a case it becomes edematous and swollen, and a vicious circle is established that can be overcome only by surgery.

Inflammation. BALANOPOSTHITIS. The common term "balanitis" means inflammation of the glans penis, but "balanoposthitis," which includes in its etymology inflammation of the prepuce, is much better, as the glans is seldom inflamed without involvement of its preputial covering. This condition usually follows phimosis, which prevents proper cleansing of the glans and promotes accumulation of smegma. It may be complicated by infection from a venereal discharge. Sometimes it affects old men who have lost interest in personal hygiene, but it is more usual in the case of boys.

Following circumcision, in such cases, the ablated prepuce is swollen and has a bright red inner surface that may show a coating of pus and a little fibrin. Microscopically the picture is rather startling in the intens-

ity of the acute inflammation that is revealed. There is widespread infiltration by polymorphonuclear leukocytes with much edema and all the characteristics of acute suppurative inflammation.

HERPES Herpetic eruptions in the coronary sulcus constitute a form of true and specific balanitis, but they are of no surgical pathologic importance unless they occasion mixed infection and invasion of the underlying glans.

CHANCROID This ulcerative lesion usually develops on the coronary sulcus and is caused by *Haemophilus ducreyi*, the Ducrey bacillus. It is a seropurulent lesion developing quite superficially and ulcerating within a few hours of its inception. The ulcer is serpiginous and spreading and often becomes secondarily infected, producing a phagedenic or erosive lesion that sloughs extensively and may become gangrenous and foul. The lesion is venereal and also affects the female vulva, where it may cause disastrous gangrene. The chancroid sometimes causes acute lymphadenitis in the inguinal glands, where buboes (familarly known as "blue balls") develop, suppurate, and break down. Microscopic lesions in this malady are not very characteristic, both ulcers and buboes exhibiting ordinary acute inflammation in which the intracellular, gram negative, dumbbell shaped bacteria may be demonstrated. If the lesion occurs in conjunction with luetic chancre it is spoken of as "mixed chancre."

INFECTIOUS GRANULOMA *Tuberculosis* This is relatively rarely observed, although it may be found as a sequel to tuberculous urethritis or to direct infection by tuberculous sputum. *Lupus vulgaris* is even more rarely noted.

Lues The primary chancre of syphilis is, of course, usually found on the glans and rather oftenest in the sulcus. It begins as a small acuminate, reddish papule and changes into a hard, button like lesion that is of rubbery consistence and may be slightly redder than its surroundings. It varies in size from a few millimeters to a centi-

meter or so in diameter. There may be shallow ulcerations on its surface from which a thin, watery fluid exudes, under darkfield illumination this will be seen to be swarming with treponemata in active motion. The inguinal lymph nodes soon become swollen and indurated, but both the chancre and these buboes are painless.

The microscopic picture of primary lesions is not strikingly specific, as it reveals a granuloma that contains large numbers of lymphocytes and monocytes with very occasional giant cells. The most specific feature is the swelling and proliferation of the vascular endothelium of the smaller capillaries and not infrequently an angitis of the larger vessels, in the walls of which wandering polymorphonuclear leukocytes are found. Fibrosis supervenes, but the resulting scar soon shrinks and may become almost imperceptible.

Lymphogranuloma Venereum The primary lesion of this venereal disease is very inconspicuous, consisting of a shallow ulcer a few millimeters in diameter that develops on the glans penis (or on the clitoris or labia minora in the female), and it is frequently overlooked. It is moist and sluggish, and it may be herpetiform. Microscopically noted, this lesion, like that of lues, is not very specific. It reveals a thickened epithelium overlying an edematous stroma in which there are numerous lymphocytes, plasma cells, and monocytes. The lesion in the inguinal lymph nodes of both male and female shows a fairly characteristic granulomatous appearance which has been described with granulomas in general (see p. 28).

Peyronie's disease or "penile strabismus," which consists of a nodular thickening of a portion of the dorsal fascia of the penis, is described in the chapter on Muscular and Adipose Tissue.

Tumors Fibroma, lipoma, and angioma of the glans are rare. Epithelial growths, on the other hand, are quite common, but it is often questionable whether they consti-

with a small central orifice. Congenital strictures may be observed in the penile urethra, or there may be atresia with complete lack of canalization.

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tute tumors or represent lesions due to viral infections.

VERRUCA. Ordinary epidermoid papillomas occur on the glans, particularly if it is unclean. There is no need for describing them minutely, for they resemble any hyperkeratotic papilloma.

CONDYLOMA ACUMINATUM ("VENEREAL WART"). This appears in the form of multiple, cauliflower-like growths on the glans and in the coronary sulcus. It occurs in the presence of any irritating discharge and is not necessarily connected with urethritis, although it most frequently follows it. The fact that simple surgical removal with a knife often leads to recurrence and a wider spread that indicates "seeding-out" of the growth indicates that it is possibly of viral origin and similar to the Shope-Rous papilloma of rabbits. On the other hand, removal by cautery or high-frequency "electric scalpel" prevents recurrence.

The microscopic picture of this growth differs from that of the ordinary verruca inasmuch as there is a piling up of epithelium in the middle rather than in the outer layers of the epidermis. This is an acanthosis, rather than a keratosis. The epidermis is thrown up into acuminate, gourd-shaped processes that may be rounded in some instances. There is no invasion of the underlying tissue, and the lesion is distinctly of a nonmalignant type.

MALIGNANT GROWTHS. Sarcomas are infrequently noted, but carcinoma of the epidermoid type is common. It needs no detailed description, as it resembles any carcinoma of this type, except that it is more papillary in its architecture. A large, cauliflower-like growth eventually develops on the glans, which it destroys. It invades the underlying tissue, working up the shaft, which it may convert into a large globular mass of fungating carcinoma. In spite of its formidable appearance, the tumor is not among the more malignant forms of epidermoid carcinoma, as it grows slowly and metastasizes to the inguinal lymph nodes

in only approximately one-third of the cases. The tumor may spread over onto the scrotum and involve it as well, or there may be "contact" metastasis between the penis and the apposed integument of the scrotum.

Treatment. Carcinoma of the penis is in a position where it can readily be treated with x-ray in caustic doses. Patients usually refrain from seeking medical advice, however, until the tumor has become very large. By that time it may exhibit considerable secondary infection, which is unfavorable for the action of the x-rays. Thus surgery appears to be the method of choice. These carcinomas require heavy dosage of x-ray therapy.

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PLATE VII



15

(Top) Fetal adenoma of thyroid This is a large adenoma as these tumors go. It resembles a kidney in some respects and is very substantial and solid, with little central degeneration. Such adenomas often undergo extensive necrosis and may contain much gelatinous colloid. This one is of the solid, parenchymatous type.

(Bottom) Thyroid with somewhat nodular hyperplastic goiter. One lobe has been bisected and sectioned surface of the two halves is shown. It is pale and firm, resembles raw fish flesh or pork, and (in this instance) exhibits nodules of lymphoid infiltration and hyperplasia.

Organs of Internal Secretion

THYMUS

DEVELOPMENT AND HISTOLOGY

THYMUS IN MYASTHENIA GRAVIS

TUMORS (THYMOMAS)

PITUITARY GLAND (HYPOPHYSIS CEREBRI)

DEVELOPMENT AND HISTOLOGY

TUMORS

PINEAL GLAND (EPIPHYSIS CEREBRI)

THYROID

CONGENITAL MALFORMATIONS

THYROID (Continued)

CRETINISM

MYXEDEMA

GOITER

INFLAMMATION

METASTASIZING THYROID TUMOR

TUMORS

PARATHYROID GLANDS

SUPRARENAL GLANDS

CAROTID BODIES

Some of these organs are perforce discussed elsewhere in this book: the islets of the pancreas, the interstitial glands of the testes, and the ovarian elements necessary for the production of estrone and progesterone are necessarily parts of organs that must be considered and grouped according to their external secretions. There are a number of glands, however, which are ductless, secreting directly into the circulation, and which, therefore, should be described as separate entities. These are the thymus, the pituitary or hypophysis, the pineal gland or epiphysis, the thyroid, the parathyroids, the suprarenals, and the carotid bodies. Although the thymus is sometimes grouped with the blood-forming organs, its function is one of internal secretion.

THYMUS

The chief interest of the thymus, in surgical pathology, has to do with its relationship to myasthenia gravis and with tumors which develop from its various cellular constituents. From the standpoint of trauma and developmental defects it is relatively uninteresting, and most of its inflammations are of little importance to us here. Investigation of the gland is warranted, during life, only when there is some promise of

alleviating myasthenia gravis or of removing tumors, for its situation in the mediastinum makes operative procedures quite serious.

The gland is derived from primordia in the same general region as those which give origin to the parathyroids and considerably more laterally situated than those that develop into the thyroid. As it originates from the third and fourth branchial clefts in the neck, it may leave vestigial remnants along the course of its migration down into the thorax, and these may be excised by the surgeon under the impression that they represent pathologic lymph nodes or possible tumors. They are readily recognized in microscopic sections by the presence in them of Hassall's corpuscles.

The size of the normal thymus is a subject of perennial dispute; it should weigh about 13 Gm. at birth and attain a weight of 35 Gm. at puberty. Most of the organs examined are obtained at autopsy after illness has exerted a strongly atrophic influence upon them; therefore, when tables are constructed to indicate the normal weights of the thymus, those based upon findings in normal individuals dead from accidental trauma will run much higher than will those founded upon figures ob-

tained at necropsies performed on patients dying from infections or other illness. There is no good purpose to be served by giving the tables here, they may be found in almost any textbook of pathology, it is merely necessary to warn the reader that an apparent hypertrophy of this organ should be carefully checked against normal weights before recognizing it as true hypertrophy.

The thymus develops early and increases in size and weight during childhood, when it appears to have its functional season, reaching a maximum at about the eighteenth year and then slowly involuting and becoming replaced by adipose tissue in which a few thymic remnants may persist for a long time. Again, one should be cautious in overestimating the importance of such rests, particularly in young adults.

The supporting framework of the gland is a reticulum composed of large cells that have anastomotic processes and produce reticular fibrils. The cells are derived not from the mesenchyme, but from the ectoderm, and hence they are epithelial. Here and there they become associated into spheroids of concentrically arranged elements that form bodies reminiscent of the "pearls" in an epidermoid carcinoma. They exhibit basophil granules, intercellular bridges, and a tendency toward keratinization, particularly when they come to lie at the center of these bodies, or Hassall's corpuscles. Therefore they are distinctly epidermoid. At the center of these onion-like bodies there is frequently degeneration amounting to aseptic necrosis, which attracts polymorphonuclear leukocytes and has the appearance of a small abscess. Such foci ultimately undergo calcification. About the periphery of the gland are lobulated masses of lymphoid tissue that show a tendency not to form follicles, but to be composed of ungrouped masses of lymphocytes. Formerly these were considered as 'thymocytes' of ectodermal origin, it is now generally believed that they are true lymphocytes which migrate into the thymus as it develops and ultimately constitute

more than one half of its tissue. There are also numerous large eosinophil cells that are seldom mentioned, they are larger than those of the circulating blood, possess large and simple nuclei, and appear to represent true thymic elements.

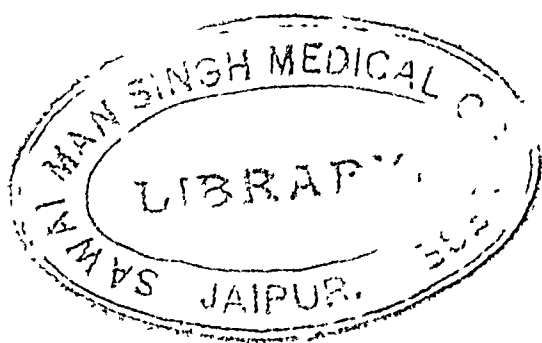
The organ has a thin capsule and rather indefinite septa containing a peripheral or cortical zone of lymphoid and a medullary



Appearance of persisting thymus in adult suffering from myasthenia gravis. It is juvenile in appearance and would be creditable in a child of 14. Thymic corpuscles show considerable degeneration.

mass of the reticuloid thymic tissue through which the Hassall's corpuscles are scattered at random. The vascular supply of the thymus is rich but unremarkable.

Myasthenia Gravis. In this disease, characterized by inordinate muscular fatigability and cachexia, one may find simple enlargement of the thymus, or no demonstrable change, or a conversion of the organ into a nonmalignant tumor composed of small cells like lymphocytes but possessing more cytoplasm than do these. Occasionally malignant tumors may be associated with the disease. Thymectomies are being resorted to with increasing frequency in this connection. At one time Crile advocated thymectomy in connection with hyperplastic goiter, but this procedure has not been taken up with any enthusiasm.



shows only elements that could be accounted for on the basis of the primitive thymic cell alone

The gross appearance of these various microscopic types of tumors is not at all characteristic of any particular type, although it definitely points to thymic origin. Any large tumor of the anterior mediastinum that lies in intimate relationship to the great vessels and trachea, often embracing them in its tissue, should be suspected of having arisen in the thymus. The malignant tumors are almost invariably stony hard and leathery, firmly adherent to the great vessels, and often spreading down over the pericardium. Widespread or telemetastasis is reported in a little less than half the cases, usually the tumor is locally invasive, particularly involving the pericardium and the lungs, to which it metastasizes more or less locally. Naturally the surgeons attempt to take biopsies from such tumors before operating, aspiration biopsies are seldom very satisfactory, as the growths are so hard and fibrous that it is difficult to detach enough tissue to make a smear or a section. It should be noted that the sarcomatoid tumors occur in children, together with the teratoid group, while the carcinomas are noted in elderly people in the "cancer age."

Operative removal of noncancerous thymomas has been successful in some instances, but their intimate association with the great vessels makes it almost impossible to eradicate them entirely. The malignant thymomas might be set down as inoperable, as they not only involve the same structures but spread into the pericardium as well at a very early stage in their development. Irradiation with the x ray has been astonishingly successful in one or two cases in our hospital, but the follow up history is as yet too brief to make any definite prognosis as to the ultimate value of the treatment. At all events, as there is nothing else one can do, irradiation is "Hobson's choice" and should be tried out

PITUITARY GLAND (HYPOPHYSIS)

Situated at the base of the brain and lodged snugly in the sella turcica, this gland is a relatively small one, but its activity and importance to the body as a whole are entirely disproportionate to its insignificant size. As it is formed by the conjunction of elements that grow downward from the infundibulum and upward from Rathke's pouch, there may be slips in the amalgamation of these and ample opportunity is afforded for congenital malformations. Thus a remnant may remain near the fossa of Rosenmüller in the pharynx, or accessory hypophyses may be found along its line of development.

Inflammatory changes of the hypophysis are of little importance in surgical pathology.

Tumors. The "strumas" and tumors of the pituitary gland are of decided interest, as they cause widespread dysfunction of various types. The hypophysis may become compromised by neighboring meningeal growths (discussed under the Nervous System) or it may be invaded by chordomas (rare tumors treated in the chapter on Cartilage and Bone).

ADENOMA. These involve adenomatoid changes in the pituitary that often involve the entire pars anterior. They may be in the form of adenomas or they may constitute areas of adenomatoid hyperplasia that are less suggestive of being true neoplasms.

Before the matter is discussed further it would be well to review in brief the composition of the pituitary. This has an anterior portion composed of glandular complexes that originate in the pharyngeal portion of the primordium, an intermediate one that is partly glandular and partly nervous, and a posterior part that is purely nervous and represents the downgrowth from the brain. The gland is attached to the latter by the infundibulum. Both the infundibulum and the pars posterior give rise to tumors which will be discussed in the chapter on

Tumors. These are divisible into the non-cancerous and the malignant groups, but as their origin is still obscure the term "thymoma" has been applied to all of them as an admittedly temporary and makeshift nomenclature.

NONCANCEROUS THYMOMA. There are two general types of this tumor: (1) one which grows to enormous size (we have reported one that weighed 2,235 Gm.) and is composed of islands of more or less disarranged, fairly normal-looking thymic tissue scattered through a vast matrix of ordinary fat; and (2) tumors comprising small cells that are slightly larger than lymphocytes and show more cytoplasm, although their nuclei are of about the same size and tend to be more pyknotic than those of the lymphocytes. These cells lie in a disorderly mass throughout the tumor, may show occasional mitotic figures and may differentiate and associate themselves into rudimentary Hassall's corpuscles. Both types of this group may be associated with symptoms of myasthenia gravis, but they may exist quite independently of this, as was proved by our gigantic example which produced no symptoms other than shortness of breath on exertion.

MALIGNANT THYMOMA. Several types may be recognized in this group, and it would be well to adhere to Symmers' classification in describing them.

1. *Lymphocytic ("Thymocytic") Type.* This is on the borderline between the non-cancerous and the malignant groups. It is composed of disorderly masses of small cells that tend to be more hyperchromatic than lymphocytes. Probably it represents a less malignant form of lymphosarcoma than the lymphoblastic type.

2. *Lymphoblastic (Large-celled) Type.* In this the cells are spheroidal or ovoid and larger than those of Group 1; they may represent either lymphoblasts or altered cells of the thymic reticulum; apparently both hypotheses are tenable. In one case one is dealing with a lymphoblastic lymphosarcoma of the thymus and in the other with

a tumor of the epithelial reticuloid cells of the organ. Although they look almost alike, one type will stain in the fashion of lymphoblasts with the Romanowsky methods, while the other will usually exhibit some areas where there is an epithelioid form of growth.

3. *Thymic Reticuloid-cell Type.* In this the reticuloid cell is no longer so primitive as to imitate the lymphoblast in its appearance; it exhibits pleomorphism and its shape varies from spheroidal to fusiform; multipolar or stellate varieties are noted. This is probably the most frequently encountered type. It may exhibit a few duct-like structures and thymic corpuscles.

4. *Perithelial Type.* This has been reported chiefly by Symmers; it exhibits a definitely perithelial arrangement of radially directed fusiform cells and is quite characteristic in its appearance. Thymic corpuscles are rarely noted in this variety.

5. *Granulomatous Type.* Symmers includes Hodgkin's disease of the thymus in his classification of thymomas, but this inclusion is questionable as it merely refers to the local manifestation of a generalized lymphogranuloma in the lymphoid tissue of the thymus.

6. *Epithelial or Carcinomatous Type.* This, most often noted in elderly subjects, closely resembles an epidermoid carcinoma, as it produces bodies that simultaneously resemble epidermoid pearls or Hassall's corpuscles. The ectodermal far outnumber the mesodermal elements. Schmincke has included this tumor in his large group of "lympho-epithelioma," in which he also places the tumors described above under Group 3.

7. *Teratoid Type.* In young children there is a type of malignant thymoma that combines with the general characteristics of Group 3 a large number of duct-like, epithelial structures which may even imitate glands. The cells may form cords that branch and interlace and that are supported by a neoplastic stroma of the large reticuloid cells. This is not a teratoma, as it

functions of the pituitary and the hypothalamus which will give rise to Frohlich's syndrome, with adiposity, retarded sexual development, and high sugar tolerance, at least some of which may be laid to dysfunction of the hypothalamus. In adults there may be much less in the way of symptoms, unless the condition develops during childhood and progresses slowly into adulthood.

stroma so insignificant that it is difficult to make out. So loose and haphazard is its architecture that one hesitates to call it an adenoma, the presence of a few chromophobe and basophil cells scattered among the eosinophilic elements again attests to the fact that this is an adenomatoid hyperplasia of one element of the gland at the expense of the rest.



Longitudinal section of entire hypophysis. At one pole there is a miliary basophil adenoma which appears in the print as dark area in glandular parenchyma (Army Medical Museum 81894, acc no 116655)

The microscopic picture is one of an adenoma that is poorly organized and composed of chromophobe cells which are arranged in masses or indefinite acini and usually show some eosinophil or basophil cells scattered about the growth in small numbers.

Acidophil (Eosinophil) Adenoma. This affects the bony metabolism and the growth of the skeleton, effecting overgrowth of the bones of the face and extremities and leading to the development of acromegaly, if it involves bony growth as a whole the result is gigantism. The macroscopic appearance of the adenoma is not very different from that of the chromophobe variety, microscopically it is seen to be made up of rather disorderly masses of eosinophilic elements that have a slightly neoplastic appearance when compared with the normal pituitary acidophilic cells. These are arranged in alveolar groups supported by a

Basophil Adenoma. This, together with the syndrome that it occasions (Cushing's syndrome), was first clearly described by Cushing. Women are more frequently affected than men. Both sexes show obesity and develop a facies known politely as a "moon face" or less politely and more appropriately as a "pig face", this must be seen to be appreciated and remembered. Besides this they exhibit hirsutism, the women developing a male hirsute habitus and the men becoming more hirsute and sometimes developing a "hairy ape" appearance. Both sexes exhibit broad striae of purple, like those of pregnancy, which radiate upward and forward over the abdomen from the flanks. In women there is no deepening of the voice, however, or hypertrophy of the clitoris, as there is in connection with suprarenal tumors of the "virilizing" type, whether of the suprarenal

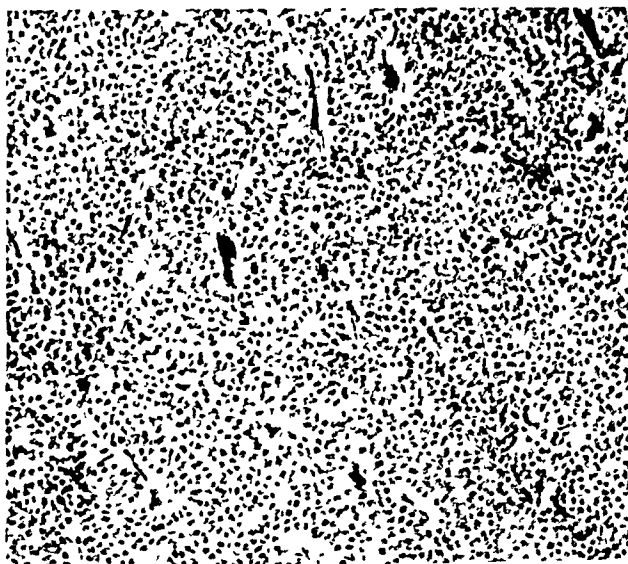
nervous system, as they are neurogenous growths.

The glandular elements of the pars anterior of the hypophysis are composed of three types of cells that are supported on a delicate stroma: chromophobe, acidophil, and basophil. The two last are, of course, "chromophil." Most good stains will demonstrate the chromophobe and acidophil cells, but the basophil elements require Bensley's stain or one of the Romanowsky group, like Giemsa's stain (q.v.) in order to be well demonstrated. Chromophobe cells have a clear, almost unstained cytoplasm; acidophil cells possess eosinophilic granules; and the basophils show basophilic granules that may be very coarse. Thus there is an analogy between the histologic elements of the pituitary and the parathyroid glands, which also show chromophobe and chromophil features. In the case of the pituitary gland any one of the three elements mentioned may become the type-cell for an adenoma.

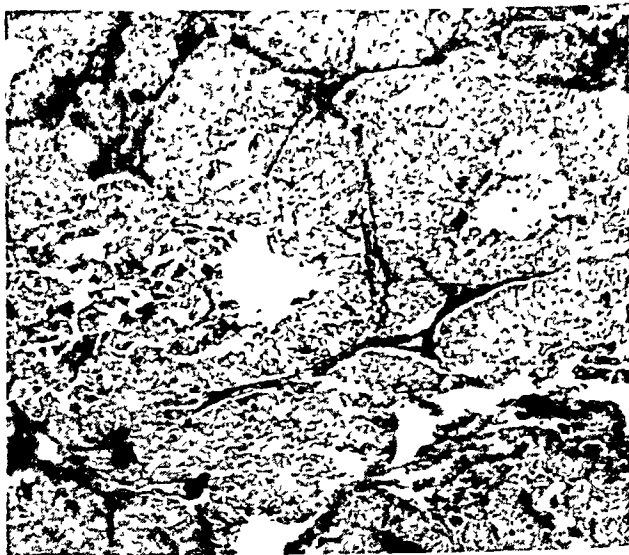
These adenomas are often called "strumas." The term has come to mean an adenomatoid hyperplasia of a gland that involves the organ without forming actual tumors, and it is used in that sense. Its real meaning in its original Latin form is "a scrofulous swelling"; this definition is very loosely applicable to the "struma thyroidea" (as the thyroid is in the neck, where "scrofula," or tuberculous lymphadenitis, often occurs), but it is sadly out of place when applied to the pituitary gland. Those who thus used it did so because it had been applied to goiters of the thyroid; some goiters are adenomatoid, hence the adenomatoid hyperplasia of the pituitary might also be termed a "struma." Although adenomatoid hyperplasia of a part of the hypophysis is not truly an adenoma, it would be better to call it one than to wander so far afield.

Chromophobe Adenoma. This is the most commonly noted type of pituitary adenoma; it may arise singly in the form of a nodule in the pars anterior, or it may take the form

of multiple nodules. In either event it is well encapsulated. Should it penetrate its capsule and impinge upon the infundibulum,



Low-powered view of chromophobe adenoma of pituitary gland. (In actual section the cytoplasm is more evident than in the photomicrograph.)



Higher-powered view of chromophobe adenoma of pituitary gland after several exposures to x-irradiation. Cells are swollen; their cytoplasm is more opaque and therefore more evident here.

however, it may cause changes in the functions of the tuber cinerium which are often attributed to the pituitary, although they more properly represent interference with the hypothalamus. In the presence of this adenoma there may thus be changes in the

and found that 65 per cent returned to work. There were 32.8 per cent 5 year cures with the transsphenoidal operation, 65.3 per cent when this was reinforced by x ray irradiation, when the transfrontal route was employed there were 57.5 per cent cures, and this was increased to 87.1 per cent when supplemented by irradiation. Radium was found to be dangerous as provoking necrosis

more epithelial, bony, and cartilaginous elements than it does nervous components, it may show adamantinomatous forms of growth. It is congenital and constitutes 4 per cent of all proved intracranial tumors. It produces symptoms during childhood, most of them attributable to pressure upon the hypophysis and hypothalamus. It may lie above or below the diaphragma sellae of



Portion of craniopharyngioma that arises in Rathke's pouch and thus straddles alimentary and nervous systems. Note cystic cavity at right, bony tissue at left, and keratinized epidermal cells entangled in marrow of bone. This is a teratoid growth.

of bone and possible meningitis. The employment of x ray alone was not favorably considered.

Acidophil adenomas have a less favorable prognosis as regards abolishment of headache and other symptoms due to compression, but they are more amenable to x ray. Ray considers these tumors to be of a type that is very likely to recur, and advises prophylactic doses of x rays at intervals of several months for some time after operation.

CRANIOPHARYNGIOMA. This growth has been mentioned in connection with the pathology of the pharyngeal vault, but it should be more fully considered here. It is a teratoid tumor that possesses a great many

the sphenoid, if below it acts like a pituitary adenoma, if above it spreads out and may involve the optic chiasm. The growth is apt to be larger than the adenomas and may extend upward in the midline or may penetrate the tentorium and gain access to the posterior fossa.

Besides symptoms and signs referable to pressure on the hypothalamic and hypophyseal region, it may exert pressure upon the ventricles and cause internal hydrocephalus. Children may fail to develop, remaining dwarfed and juvenile, they may become obese, or they may show an emaciation of the Lorain type accompanied by headache and persistent vomiting. If the disease develops during adolescence, men

cortex or of the ovary. Men become impotent and may show a flushed, tense, and painful obesity of the face. Hypertension may be observed in both sexes, with osteoporosis and diabetes; or a change in the curve of glucose tolerance may be noted. The pathologic changes in the hypophysis are in the neighborhood of the pars intermedia, into which the tumor-like growth

chromophobe cells, and their similarity to ependymal tumors may cause confusion. They are more massive than the noncancerous adenomas, showing a tendency to break out of their capsules and to invade the neighboring structures. They may also infiltrate the sinuses of the base of the skull and thus metastasize to other parts of the body. Their microscopic structure is said



Section of rib from patient with basophil adenoma of pituitary. Consistence of this bone is said to have resembled "wet cardboard," and it showed marked halisteresis. Note broken and tenuous trabeculae and widened marrow spaces. (Army Medical Museum 81893, acc. no. 116655.)

may extend. This adenoma is composed of large basophil cells that tend to be pyramidal; they radiate from papillary projections of stroma, forming slipshod acini and papillae. They may show some loss of basophilic granules.

Malignant Adenoma. Henderson indicates his belief that there are two types of these, one of them responding to x-ray therapy and the other failing to do so. He intimates that the former may be an intermediate form between noncancerous and cancerous adenomas and not a true carcinoma. The unresponsive group is "hopelessly malignant" and constitutes 1 per cent of all pituitary tumors. Unlike the other type, it is characterized by marked trigeminal-nerve involvement.

Most of these malignant tumors involve

to vary; they may be composed of solid masses and cords of atypical hypophysial cells which are usually chromophobe, although about eight instances of acidophil carcinoma have been reported. Some of them may exhibit cystic softening. An atypical form, considered by Ewing as carcinomatous, has been described; Benda (quoted by Ewing) demonstrated granules in the cells of this which indicate its epithelial nature.

Angiomas and angiosarcomas of the hypophysis are probably closely related to those of the meninges, which will be discussed with the pathology of that membrane (see Chapter 20, Nervous System).

Prognosis and Treatment of Hypophysial Adenomas. Henderson reviewed 187 of Cushing's cases of hypophysial adenomas

of smaller ones not unlike lymphocytes in their general appearance. Thus pinealomas will exhibit two type cells, rather than one. The larger elements may be more primitive and their processes rudimentary, the small cells are not much changed. Unfortunately this ready criterion for diagnosis is often lost in the malignant variety, the pineal blastoma, which presents bizarre changes in the larger elements or may be composed chiefly of the smaller ones, which may form rosettes and simulate neuroepithelioma quite closely.

As in the case of most tumors of nervous origin, surgery is a better method of treatment than is irradiation. It goes without saying that, in as inaccessible spot as the site of the pineal gland, surgery is anything but safe and easy.

THYROID GLAND

More properly called the "thyreoid," the gland is almost universally known as the "thyroid." It originates from an antero-mesial primordium that extends between the first and second pharyngeal pouches, beginning at the foramen cecum of the tongue, traversing the body of the hyoid bone, and then branching out laterally into two lobes that are intimately associated with the primordia of the thymus and parathyroids which arise laterally in the third, fourth, and fifth branchial clefts, possibly it derives some of its substance from these. As a result of this rather sprawling primordium and its association with those of the glands just mentioned, embryologic mix-ups are very apt to occur. The embryologic structure known as the "ultimo- or post-branchial body," which is not particularly important in human embryology, has been blamed for certain laterally situated tumors in the thyroid region and for embryonal rests known as "lateral thyroids."

Congenital Malformations During its maturation the primordium may not disappear as it should in the region of the foramen cecum, bits of thyroid may continue to develop here and form "lingual thy-

roids" which are subject to all the pathologic changes of normally situated thyroid tissue, or the thyroglossal duct may remain patent and become dilated into a cyst—a structure with a wall of variable thickness that is lined by epithelium and filled with mucoid secretion. The epithelium may be of a cylindrical and ductile variety, or it may be somewhat epidermoid in its type. One may then find a persistent thyroglossal duct, or a cyst, or both, these readily become infected. During their surgical removal care must be taken to search out every bit of their wall and to remove the body of the hyoid bone, otherwise they will recur and the whole operation must be repeated in the presence of scar tissue that will confuse the issue.

Accessory thyroid tissue may be found as detached fragments or as "lateral thyroids" which may lie behind the sternocleidomastoid muscles quite isolated from the thyroid proper. They differ from that gland in the microscopic appearance of their epithelium, which is wont to be cylindrical and clear rather than cuboidal and cloudy as it is in the thyroid. It may also show definite papillary overgrowth that is quite foreign to normal thyroid tissue.

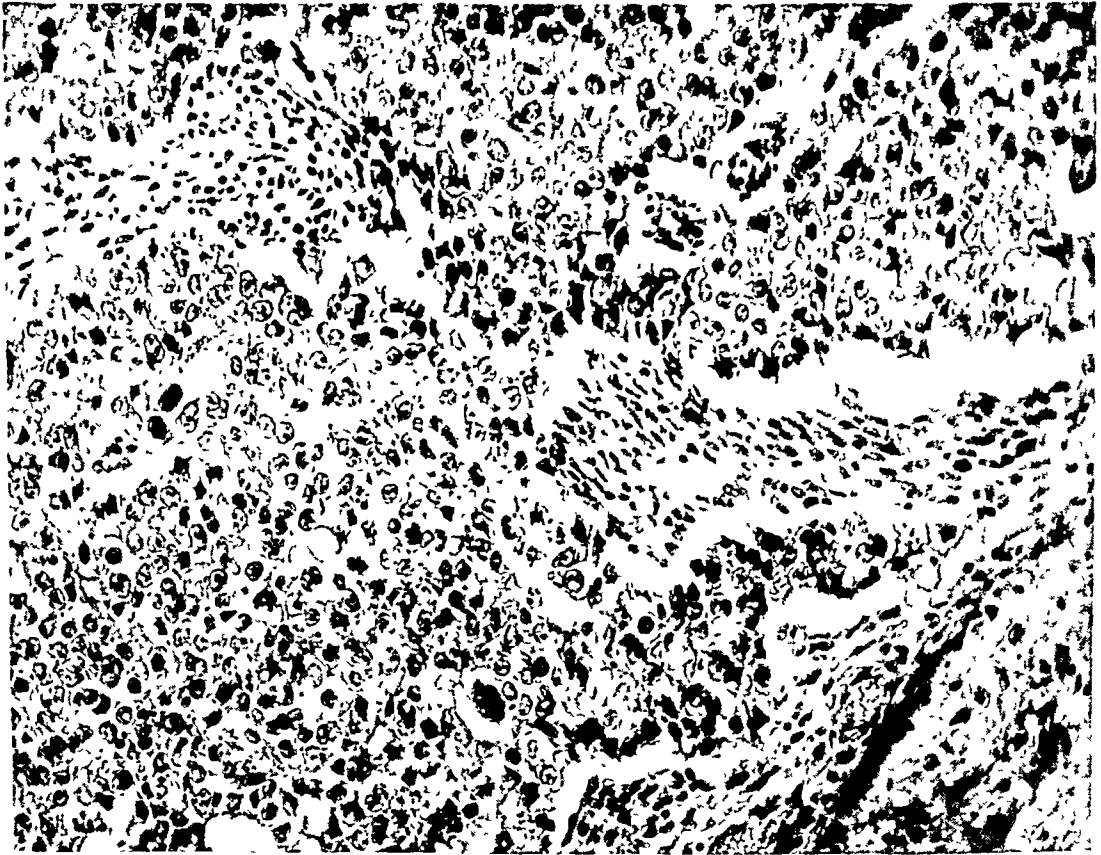
After the thyroid has developed it becomes a very labile organ that responds so rapidly to stimuli toward hyperplasia or toward involution that it is very difficult to keep up with it. It has very little stroma, and this is very vascular and insubstantial, it is filled with a soft stored secretion known as "colloid" which constitutes the bulk of the gland, lends it no solidity, and thus renders it susceptible to trauma. Finally, the thyroid is in an exposed position. Aside from these factors, the organ reacts to a number of stimuli from hormones secreted by other organs, particularly the pituitary gland. It is also affected by stimuli based upon disturbed metabolism (as in acute febrile infections) or psychic disturbances, these are as yet poorly understood. It is a fact that exophthalmic goiter was never more prevalent in our hospital than it was

struation stops in girls and libido ceases in boys, with the development of infantilism. The skin is fine and wrinkled, the hair fine and silky, and in some cases the facies have the appearance of advanced age.

Macroscopically the tumors have the appearance of teratomas; the microscope reveals that their composition is chiefly der-

physis, which is sterile ground for the surgical pathologist except in so far as it may be involved in primary tumors which are often puzzling and resemble those of the "glioma group" of the brain much more than they do glandular neoplasms.

Globus has described pineal tumors most excellently, beginning with a consideration



Field from a pineal tumor that resulted fatally. Note two types of cells: one is large and pale and forms bulky masses, the other is small and compact and is grouped into trabecular structures.

moid, with some resemblance to cholesteatoma; but there may be bone or cartilage and, as noted above, elements of the type of the dental enamel organ. One of the finest adamantinomas in our collection came from a craniopharyngioma. Surgery is the preferred treatment, and it has been found that, when the tumors are cystic, a course of irradiation with the x-ray will often cause them to shrink and thus ameliorate symptoms.

PINEAL GLAND (EPIPHYSIS)

After discussion of the pathology of the hypophysis it is logical to turn to the epi-

of the embryology and histology of the gland itself. The tumor is a bulbous, spheroidal to ovoid tumor that occupies the site of the pineal gland, replacing it in most instances and invading and distorting the neighboring quadrigeminal body. It may develop superficially from the epiphysis, displacing rather than replacing it. It usually measures only about 2 to 3 cm. in diameter. As the pineal gland is composed of two types of cells the tumor usually shows a similarity to these. Normally there are large multipolar cells, rather larger than astrocytes and with processes ending in bulbous tips; these cells are supported by a stroma

overlapping of categories. A simple table which is useful as a basis from which to work is the following which has been attributed to Marine

disturbances, have a slightly elevated basal metabolic rate, and are "touchy" and hard to get along with. They are unreasonably irritable. Grossly their thyroid is large and

	<i>Parenchymatous</i>	<i>Intermediate</i>	<i>Colloid</i>
<i>Diffuse</i>	Adolescent goiter	Goiter with nervous symptoms	Endemic goiter
<i>Nodular</i>	Seldom observed	Seldom observed	"Nodular goiter"
<i>Adenomatous</i>	Trabecular adenoma	Between the extremes of this line	Adenoma of 'long standing'

DIFFUSE GOITER *Diffuse Parenchymatous Goiter* This is a moderately enlarged thyroid that is noted in adolescent children,

colloid and looks much like that of the type next to be described, microscopically one finds the picture of a diffuse colloid goiter



Area of acinar proliferation by budding in "nervous" type of diffuse colloid goiter. Such areas alternate with widely dilated and gigantic acini. Colloid is mature and stains orange when Masson trichrome technique is used.

usually girls, in regions where the soil has been deprived of iodine. The gland is firm and noticeable on casual inspection, as it is not wittingly removed by surgical operation. It seldom comes under the purview of the surgical pathologist. Microscopic examination reveals a moderate degree of hyperplasia of the epithelium which is increased in height. Colloid is not produced in excess.

Diffuse Colloid Goiter with Nervous Symptoms Occasionally, in connection with an apparently diffusely colloid goiter, one notes patients who suffer from vasomotor

plus areas of small acini which appear to have been recently produced (presumably by budding from the larger ones) and which present a slightly higher epithelium than normal.

Diffuse Colloid (Endemic) Goiter This usually develops in regions where the soil has been glaciated and is poor in iodine. The gland may become very much enlarged, protruding in front of the neck in an unsightly manner, bulging anteriorly and laterally, and attaining a diameter of 20 to 30 cm. It is of varying consistence, as

during the depression of 1930-33, when patients were worried over finances and the accompanying familial situations. Hence the gland may be said to be in a constant state of ebb and flow of activity in individuals of a certain type. Women are more often affected than men, whose psyches appear to be more stable on the whole.

The experiments of Marine, McCarrison, Webster, and Chesney and the observations of Goormaghtigh on hyperplasia following acute infectious fevers all go to show that the gland can compensate for the loss of some of its "lobules" by hyperplasia resulting from a budding of acini that are already present, rather than from the formation of entirely new ones by mitotic division of detached thyroid cells. The word "lobules" is put in quotation marks because the septa of the thyroid, which appear to divide it into lobules, actually divide it into pseudolobules which are intercommunicating; this is demonstrable only in tridimensional reconstructions of the gland's histologic composition. Thus a given thyroid may undergo hyperplasia as a result of certain stimuli (psychic, for example), then undergo involution as the stimuli weaken or subside, only to repeat the process *de novo* when these recommence. This results in the production of nodules in which involution has been imperfect and which may show degeneration of various sorts, although they are in contact with normal thyroid all about them. The outcome of all this is a very variable pathologic picture that is difficult to describe and to interpret and even more difficult to classify; in fact, after experience with the vagaries of the pathology of this organ one is inclined to look somewhat wryly upon the glib classifications that abound in the literature.

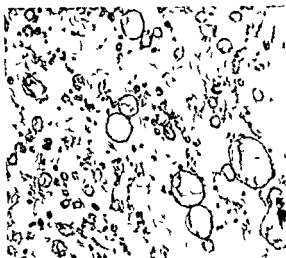
Cretinism. The thyroid fails to develop properly in the children of parents who are suffering from diffuse colloid goiter, or it may fail from unknown causes; in either event the result is hypothyroidism or cretinism. The child with this defect does not grow, it is dwarfed and fat, its facies mon-

goloid. Its tongue is large and protrudes from the mouth. Its hair is coarse, while its skin is dry and scaly, thick and wrinkled. There is retarded sexual development. The thyroid is small and almost vestigial, and under the microscope it reveals apparently active acini possessing a cuboidal epithelium that is higher than usual, but no contents that can be stained in sections. The stroma is thick and fibrous. All the signs and symptoms usually disappear in a miraculous fashion upon the administration of thyroid extract to the patient, but this must be continued indefinitely. Endemic cretinism occurs in regions poor in iodine, owing to glaciation of the soil; sporadic cretinism is less readily explained, although it may be attributed to congenital aplasia of the thyroid.

Myxedema. Adults acquire a condition similar to cretinism known as "myxedema" because the sectioned skin and connective tissue drip a limpid, mucoid fluid. It may be attributable to hormonal imbalance; its causes are vague. The patient exhibits the dry coarse skin, the coarse hair (which replaces the normal hair as it falls out), the swollen mongoloid features, and the obesity, as well as the dulled mentality of the cretin, but not his dwarfism. Speech becomes slurred and indistinct on account of the enlargement of the tongue. The thyroid undergoes atrophy and fibrosis and differs from that of the cretin in showing little or no pseudohyperplasia. The acini are poorly formed and embedded in fibrous tissue and fat. The cells may show anisocytosis, and some of them may be swollen and enlarged. A similar picture may follow prolonged bouts of hyperthyroidism, in which case it is known as "exhaustion atrophy." Sometimes there is enough metaplasia of the cells to suggest carcinoma, particularly when mitoses are found; one should guard against this mistaken diagnosis.

Goiter. It is easy to make a series of classifications of goiter, but difficult to "make them stick," as goiterous types are not clear-cut and there is a good deal of

Fetal adenomas in adenomatous goiters must be differentiated from pseudo adenomas in nodular colloid goiters, such differentiation is not always an easy matter. The lobules of nodular colloid goiters used to be known as "adenomas", when they contained true fetal adenomas one spoke of "adenoma in adenoma" (This is mentioned in case the reader might encounter the ex-



Intermediate type of adenomatous goiter ("fetal adenoma") of long standing. Note hyaline fibrous matrix which is so edematous that it is almost gelatinous on gross examination.

pression and be puzzled thereby.) There seems to be little question that the fetal adenomas are true neoplasms, they may be noted in normal thyroids, but they are much more frequent in the adenomatous and nodular colloid varieties.

HYPERPLASTIC GOITER (Graves' Disease, Basedow's Disease) Patients suffering from hyperplastic goiter undergo profound metabolic changes, the disease or dyscrasia usually occurs in women in early middle life, between the third and fourth decades. Occasionally it may be observed in young girls shortly after adolescence, and it affects men also, although not so frequently.

The patients develop a moderately enlarged thyroid that is firm and symmetrically swollen. They exhibit greatly increased basal metabolic rates that average well

above +60. They become nervous and irritable, their pulse rate rises until it is best counted by mechanical means (sphygmograph or electrocardiograph). Flushing and sweating occur, and, as the process advances, interference with the cervical sympathetic nervous system brings about protrusion of the eyeballs (exophthalmos) until, in some cases, the lids can no longer be closed over them.

There appears to be a decided psychic factor in the causation of hyperplastic goiter, as it is common in the case of those who are worrying over financial or familial matters. For example, a patient may be brought to the hospital and given a simple course of treatment by rest, upon being returned to the family circle she promptly lapses into her former state of hyperthyroidism. The reader is referred to the bibliography for further details as to the experimental and clinical investigations that bear upon the etiology of this dyscrasia.

Grossly there are two forms of hyperplastic goiter, the diffuse and the nodular, possibly the latter represents a less severe type of longer standing and one which has undergone more fluctuations than has the diffuse type. The gland is enlarged and firm, sometimes it is almost stone hard, it is usually finely lobulated and opaque gray on its sectioned surface when observed in the laboratory after it has been drained of blood. In situ at the operation it is red and turgid. The appearance of the gland on section is often likened to that of raw pork or raw fish. It may show a yellowish brown color or dots of this hue if there is much lymphoid tissue present, for lymphoid tissue is distinctly yellowish on gross inspection.

Microscopically the untreated hyperplastic goiter (which is almost never observed nowadays) is found to comprise dilated acini with papillary overgrowth of a cylindrical, rather than a normal, cuboidal epithelium, the papillae may be provided with stroma, or they may be pseudopapillae without stroma. Colloid is almost entirely ab-

portions may undergo various forms of degeneration: cystic, calcific, hemorrhagic, etc. The patients, unlike those with the preceding form of goiter, show few symptoms and are rather placid in temperament. They may exhibit signs of hypothyroid function. Diffuse colloid goiter is very common in the so-called "goiter belt" of the United States along the Mississippi and Ohio River Valleys and throughout the Alpine regions of Southern Europe. So common is it in Switzerland and the Bavarian and Austrian Alps that the patients have the prefix "Kropf" ("goiter") applied to their nicknames, e.g., "Kropfhiasl" or "goiter Johnnie."

Upon removal these goiters are found to be diffusely and evenly enlarged, at the same time being soft and gelatinous; they may show areas of cystic degeneration, and some portions of them are so insubstantial that they almost fall to pieces spontaneously, like a jelly. For this reason hemorrhages are often found scattered throughout the gland, and old blood may undergo liquefaction and produce cystic collections of fluid with thick, leathery walls enclosing a brownish fluid that is filled with glistening golden crystals of cholesterol. If such areas become organized, instead of liquefied, calcified scars are the result.

Under the microscope one finds thyroid tissue composed of enormously dilated acini with thin walls comprising flattened epithelial cells that are almost squamous and are sometimes called "endothelioid." The colloid stains normally, or it may show a few areas of degeneration and contain desquamated cells from the acinar walls. The colloid tends to "riffle" under the microtome knife and to be broken into band-like fragments that run at right angles to the line of section.

NODULAR GOITER. As noted in the table, this is almost always of the colloid type. It is very nodular and asymmetrical, often producing one large lateral mass in the thyroid, and it is the usual type in the so-called "plunging" or intrathoracic goiter. The tis-

sue of these goiters is subdivided into smaller nodules by septa of connective tissue that are often cicatricial in their appearance. They are prone to undergo cystic degeneration with hemorrhage, which may give rise to solidly calcified areas like bits of chalk or marble in the more degenerated areas. Occasionally some of the lobules may exhibit hyperplasia. These goiters probably represent the results of exaggerated cyclic disturbances in the thyroid parenchyma, with successive stages of hyperplasia and involution. Numerous areas of fibrosis and of budding of tiny acini may bring about a picture so identical with that seen in adenomatous goiter with fetal adenoma that it is unprofitable to attempt to differentiate between the two.

ADENOMATOUS GOITER. This is usually closely associated with nodular goiter and differs from it in the production of small adenomas the tissue of which closely resembles that of the fetal thyroid, wherefore they are known as "fetal adenomas." They may be congenital, or they may develop in the course of time; it is hard to decide which. They are well encapsulated; when they represent the parenchymatous form they are pinkish and granular and resemble small kidneys; when they are colloid they seem like areas of gelatinous thyroid tissue surrounded by a thick fibrous capsule.

Microscopically the trabecular type exhibits a very cellular architecture composed of closely set cords or abortive tubules and acini of plump cuboidal cells embedded in a fibrous stroma. In the colloid form there may be acini that vary from miniature examples composed of cuboidal cells to fairly large ones containing colloid. These acini are almost always separated from one another by wide bands of hyaline collagenous tissue that often resembles escaped colloid in its appearance. While it is possible that some colloid may escape from the acini into this supporting stroma, it seems much more probable that the areas resembling colloid are really very much swollen and degenerated collagenous fibrous tissue.



Hyperplastic goiter after course of treatment with Lugol's solution Note that colloid is partly dark (representing red staining) and "rippled" and partly thin (where it stains green) and still vacuolated Cells of acini are now mostly cuboidal as a result of treatment, before which they were presumably cylindrical



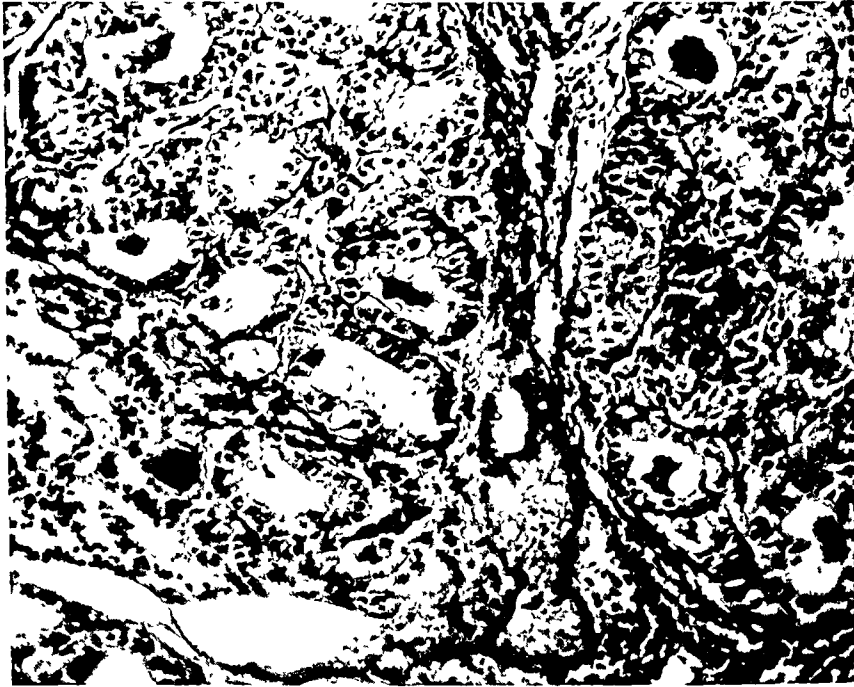
Hyperplastic goiter after treatment with thiouracil Note complete lack of involution and of any colloid storage

sent, the acini being filled with a fluid that does not take any dye. In some instances there is a diffuse lymphocytic exudate, and in the more severe and prolonged examples there are lymphoid follicles which may be very prominent in the "yellowish thyroids" already mentioned.

Because of surgical disasters in removing thyroids from patients in the full flower of

greenish and normally gelatinous colloid stains orange. Thus one gains a standard for judging the efficacy of courses of Lugol's solution or hydriotic acid by reporting the microscopic findings.

Very recently a new method for treating hyperthyroidism has come into being with the introduction of thiouracil, a urea compound. While this affects amelioration of



Hyperplastic thyroid in exophthalmic goiter. Colloid is un-substantial, vacuolated, and eroded or scalloped at its margins. Cellular hyperplasia is manifest.

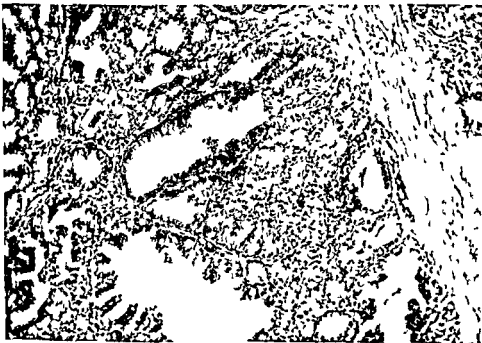
hyperthyroidism it has been found that they may be prepared for operation by a course of iodine therapy which overcomes most of the symptoms temporarily, but long enough to quiet the patient for operation. Under these circumstances the microscopic picture is less strikingly abnormal. The epithelium may return to a normal cuboidal type, with only a few acini revealing the cylindrical form. The colloid begins to be formed in the acini and may attain almost normal appearance, staining orange or red in the Masson method and showing a variable amount of peripheral scalloping and vacuolization; or it may not "involute" to this extent, in which case it will stain greenish. This apparently depends largely upon its consistence; liquid colloid stains

the symptoms of hyperthyroidism, it does so outside of the thyroid gland, which continues to show hyperplasia or even an exaggerated form thereof in which mitoses may be found in the overactive epithelium. There is as yet very little literature on the subject; let it suffice to point out that there will be little change in the histology of thyroids from patients treated with this compound. When examining thyroids from patients with hyperthyroidism it is always best to take a number of blocks of tissue from several widely separated parts of the gland in order to gain as wide a survey as possible of the changes in the organ.

EXHAUSTION ATROPHY OF THYROID. It often happens that a surgical specimen of thyroid will show a peculiar picture under



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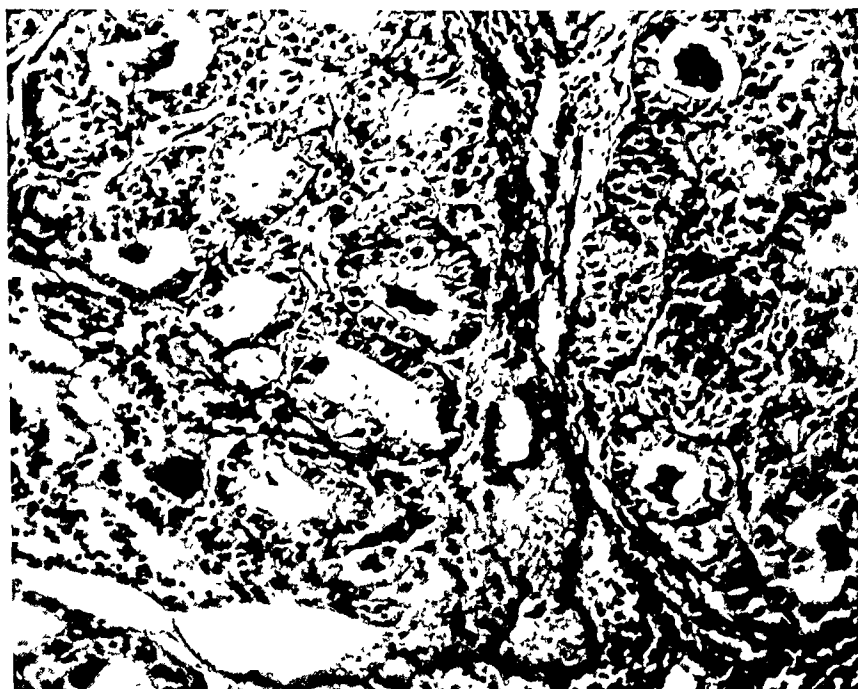
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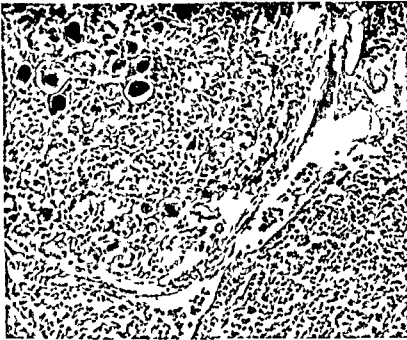
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This is so marked as to give the condition its name, "struma lymphomatosa." The term is not too happily chosen as "struma" means a "scrofulous swelling" and "lymphomatosa" means lymphomatous. To anybody meeting it for the first time this would suggest some connection with swollen tuberculous lymph nodes, which would be en-



Typical picture of struma lymphomatosa. Note lymphocytic infiltration of parenchyma and the collection of lymphoid tissue at lower right

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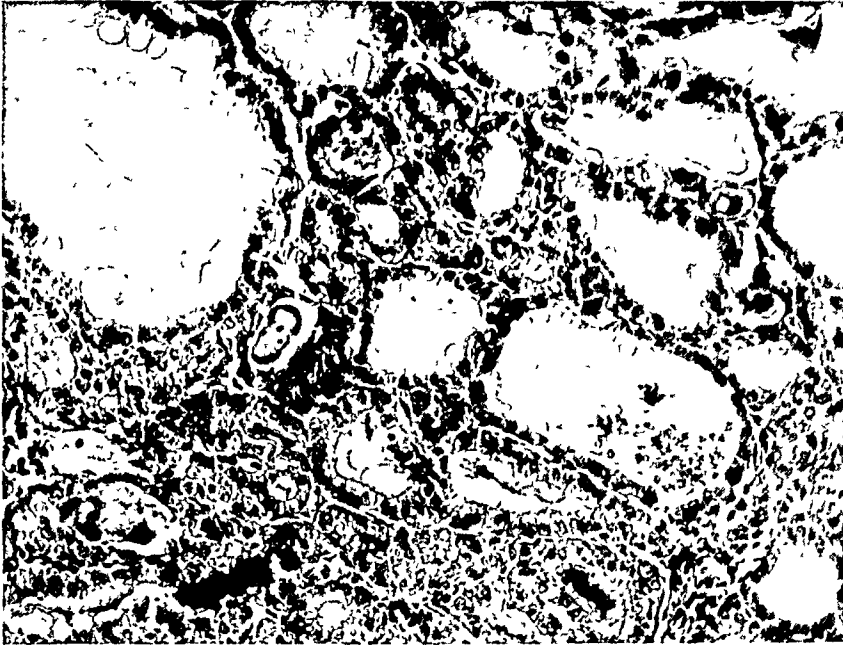
Microscopically the acini are found to vary in size and appearance, their epithelium may reveal a characteristic "ground glass" look, there is swelling of some cells, shrinkage of others, in some acini there may be masses of inspissated colloid that may be basophilic, while others contain desquamated epithelium or foreign body giant cells. Scattered throughout the stroma there is a large amount of lymphoid tissue, either in the form of a cellular infiltrate or, more importantly, as lymphoid follicles

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The cause of lymphomatous goiter is quite unknown, it has the appearance of an end product of prolonged hyperthyroidism, in which the thyroid often accumulates prominent amounts of lymphoid tissue. The history of the patients almost uniformly fails to present any evidence of past hyperthyroidism, however. Another theory is that it is the early stage of Riedel's struma, this theory was quite popular for a time, but that disease occurs in both sexes and at an earlier age, while cases of struma lym-

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STRUMA LYMPHOMATOSA (HASHIMOTO'S DISEASE). Enlargement of the thyroid with induration of the organ and marked adhesion between it and surrounding structures may occur in women near the menopause. The enlargement gives no symptoms or signs unless it compresses the trachea or interferes with laryngeal innervation, bringing about hoarseness and discomfort in



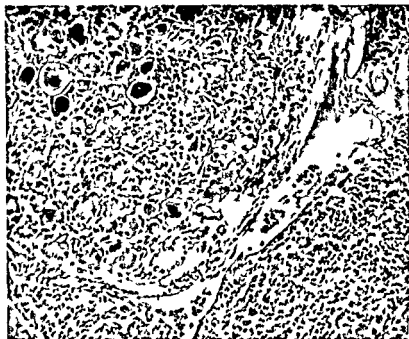
Hyperplastic goiter showing exhaustion atrophy. Its cells are metaplastic, swollen, and cuboidal. Some show hyperchromasia. Mitotic figures may be found here and there and may mislead pathologist into erroneous diagnosis of carcinoma.

be present, and the pathologist may fall into the error of making a diagnosis of carcinoma. The colloid is immature, scalloped, and often very scanty in amount. There may be lymphocytic or lymphoid infiltration of the gland. The condition, in reality, represents an attempt on the part of the tissue to keep up the overactivity that is incidental with prolonged hyperplasia. This results in the changes just described, and the condition is best termed "exhaustion atrophy," although it is familiarly known as "burnt-out thyroid," which is at least an expressive term. The pathologist should always be careful to recognize this state of exhaustion and not confound it with early malignant degeneration.

breathing. Patients have been known to consult a laryngologist in the impression that there was something wrong with their vocal cords, or because of a hacking cough attributable to interference with laryngeal innervation. In such patients the basal metabolic rate is low and may be normal or subnormal; it is seldom higher than $+12$. Men are not supposed to suffer from the disease, and Hashimoto made this very clear in his original article in 1912. In our hospital, where a survey of cases was made by McSwain and Moore, it was found that struma lymphomatosa constituted 1 per cent of thyroid disease in the department of surgery. Their paper affords an excellent review of the subject with ample references.

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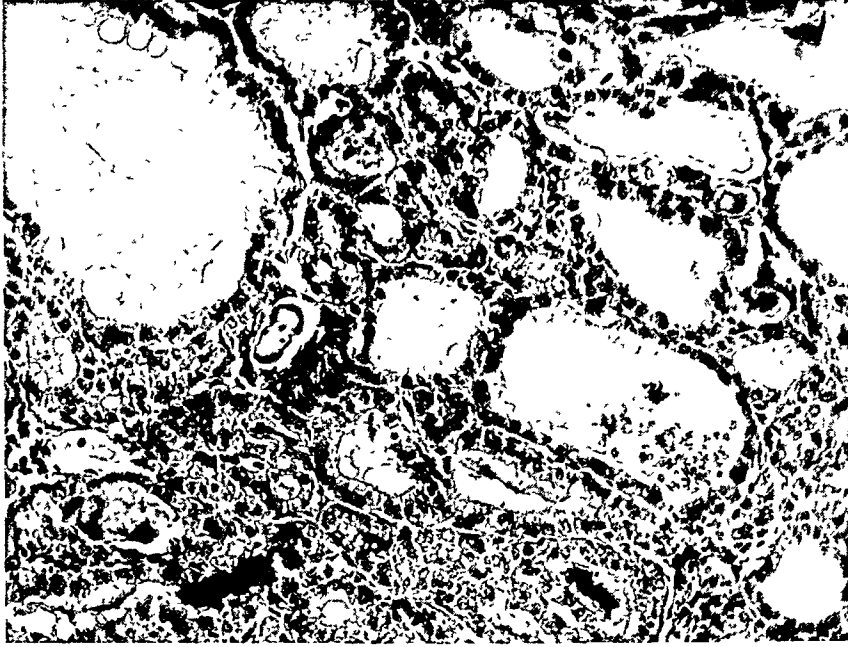
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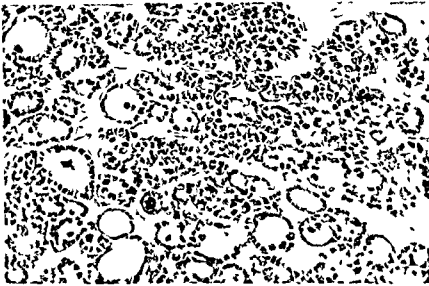
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Primitive embryonal adenoma of thyroid There is no tendency toward formation of papillae Cells are eosinophilic and may indicate the origin of those larger eosinophilic elements in so called "Hurthle-celled tumor" of thyroid

Metastasizing Thyroid Tissue Apparently normal thyroid tissue may metastasize, on rare occasions, to distant parts of the body: lungs, liver, and bony skeleton This is one of those things that must be observed personally to be believed, and one may see it but once in a lifetime To the naked eye the metastatic foci look like thyroid tissue, and under the microscope they prove to differ very little from it, there is not the slightest indication that they are neoplastic aside from the fact that they are circumscribed lesions composed of thyroid tissue which are completely foreign to the organs in which they are found Colloid goiters may exhibit similar metastatic habits Such metastases are ultimately fatal, and the only analogy one can produce for such unorthodox behavior on the part of normal tissue is the observation of metastases from apparently noncancerous chondromas to the lungs

Tumors NONCANCEROUS GROUP These are chiefly adenomas, one of which (the fetal adenoma) has already been discussed

Embryonal adenoma There is a form known as the "embryonal" adenoma which looks like the fetal adenoma when viewed with the naked eye, but differs from it un-

der the microscope Grossly it is apt to be yellower and more opaque than the fetal type and to lack its granular, pinkish parenchyma Under the microscope two sub-



Papillary adenoma of thyroid composed of clear cylindrical cells which probably have their origin in lateral thyroid rests

types may be recognized the solid type, which shows compact alveolar masses of rather high, clear cells, and the papillary cystadenoid type, which is composed of similar cells arranged about the walls of cystic spaces into which papillae usually project In young children the second type

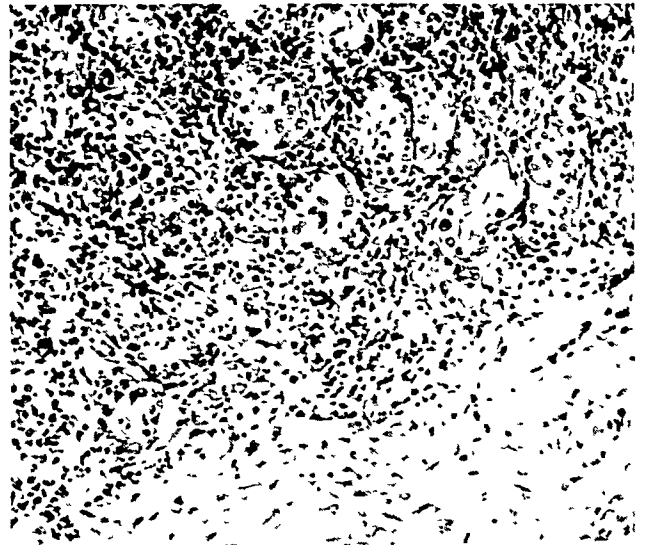
phomatosa have been followed over a period of several years and found to remain true to type and not become converted into Riedel's struma.

Inflammation. ACUTE THYROIDITIS. This may occur in connection with acute infectious diseases and result in abscess of the thyroid; it may be found in the newborn and in adults as an extension of local infection in the neck.

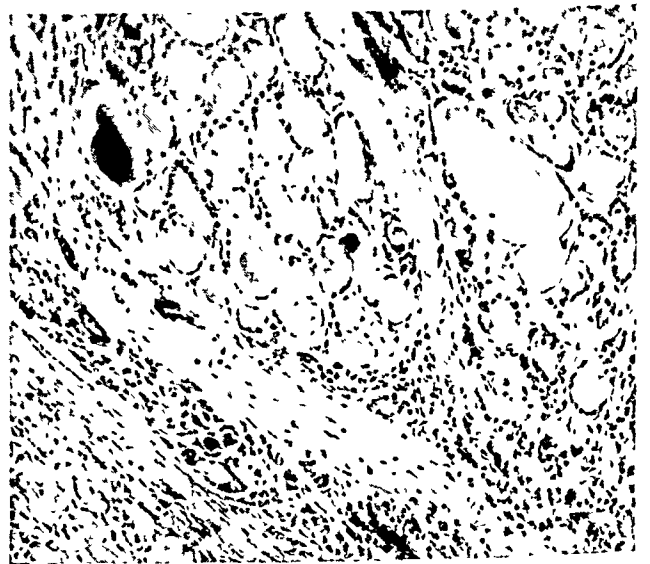
INFECTIOUS GRANULOMA. Tuberculosis may invade the thyroid, but it is very easy to mistake involutional phases of goiter with foci of giant cells for tuberculosis. Careful stains for tubercle bacilli should be resorted to unless extensive caseation makes the diagnosis unmistakable. Syphilis is rarely observed as gumma of the thyroid or as an interstitial thyroiditis in young children.

CHRONIC THYROIDITIS (RIEDEL'S STRUMA, LIGNEOUS STRUMA). The most important type of chronic inflammation is the lesion known as "Riedel's ligneous or 'eisenharte' struma." (This was mentioned above in connection with struma lymphomatosa.) In this lesion there is a progressive fibrosis that may be accompanied by a variable amount of lymphocytic infiltration. It occurs in younger age groups than does Hashimoto's struma and involves both sexes. The lesion may be bilateral or unilateral, symmetrical or asymmetrical, and it consists of an enlargement of the thyroid through proliferation of fibrous tissue in the form of thick leathery bands that traverse the gland in all directions and split it up into small lobes of surviving thyroid tissue. The fibrous tissue is like sole leather, rather than wood or iron. The microscope demonstrates that the fibrous tissue is partly collagenous tissue of an acellular type and partly young and cellular tissue containing many youthful fibroblasts. The parenchyma exhibits changes that are in the main similar to those enumerated for struma lymphomatosa, with a good many lymphocytes and plasma cells in the stroma, but the chief lesion is a rather pure example of what

might be termed a "strangling" fibrosis, in which the constantly increasing fibrous tissue literally squeezes the parenchyma out of existence.



Early lesion in thyroid affected by Riedel's struma. Note atrophic acini, numerous and diffusely scattered lymphocytes, and advancing band of fibrous tissue at lower margin.



Field from Riedel's (ligneous) struma. Note heavy fibrosis at lower left corner and scattering of lymphocytes throughout stroma of gland.

The disease is uncommon, only three instances having been noted in our hospital since 1932. It must always be distinguished from carcinoma, which it may resemble both in its clinical signs and its gross appearance.

failed the only remedy is recourse to x ray therapy, which is of doubtful permanent value

Small Alveolar Large celled Carcinoma (Hurthle cell, Langhans', Postbranchial Struma) A tumor of many aliases, this growth appears to be malignant or not malignant according to circumstances. Ewing named it the "Hurthle cell tumor" because he considered that it contained cells



Clear celled papillary adenocarcinoma probably arising in papilloma and invading thyroid, some of normal tissue of which is seen running diagonally across field

of the interstitial tissue of the thyroid of lower animals which was discovered by Hurthle. Later he adopted the term used to head this paragraph, indicating that he considered it to be a malignant neoplasm. It cannot be recognized on gross inspection. It tends to be rather sharply delimited. Microscopically it is composed of two types of cell, a large, finely granular, and strikingly acidophilic variety and smaller cells with clear cytoplasm and a polygonal outline. The components are quite irregular in their outlines and are fitted together like the pieces of a jigsaw puzzle. From its prominence in the literature one might expect this to be a common tumor, but actually it is rarely seen.

Other Carcinomas of the Thyroid These run the gamut from poorly defined adeno-

carcinoma to simple or solid types. They are apt to produce a single well encapsulated mass of rather grayish and opaque tissue.



An atypical, small celled carcinoma of thyroid which would never be mistaken for lymphosarcoma, as are the more typical varieties.



Carcinoma developing in a banal fetal adenoma of thyroid which, on gross examination, looked like any other non malignant adenoma. Microscope reveals carcinomatous metamorphosis, illustrating advisability of routine microscopic examination.

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Microscopically these carcinomas may be glandular, forming acini and secreting colloid, or they may have large cylindrical

Organs of Internal Secretion

They exhibit numerous mitotic figures and are intimately associated with neighboring lymph nodes which it appears to invade. This raises the question as to whether tumor and lymph nodes have developed together as a congenital malformation, or whether the tumor is malignant and metastasizing to the nodes. The former hypothesis appears to explain the situation best, but more data will be needed before a categorical statement can be made.

Both types of embryonal adenoma are proposed by some authorities to be derived from the lateral thyroid primordium, possibly from the ultimobranchial body. The second type may exhibit considerable lymphoid tissue, which possibly lends weight to the hypothesis of branchial origin. It may also contain a great deal of brownish pigment in its stroma and in giant cells in the acini; this is probably a product of hemorrhage, and it gives a positive reaction for iron and therefore hemosiderin. While the first type of adenoma secretes little or no colloid, the second may produce it abundantly.

Connective-tissue and Other Tumors. These are decidedly rare and will be passed over with mere mention. Chondromas, sarcomas, and occasional teratomas may be observed; the latter exhibit dermoid tissue, cartilage, and bone.

CANCEROUS GROUP. Carcinoma of the thyroid produces very hard tumors that are densely adherent to the surrounding structures and often invade them in a quite unhesitant fashion. They all look very much alike, and it is only under the microscope that they can be diagnosed, indeed they occasionally simulate Riedel's struma so closely as to be recognizable only when viewed microscopically. They metastasize widely in some instances, remaining localized in others. When they arise lateral to the thyroid they infiltrate the sternocleidomastoid muscle and are in close proximity to the carotid vessels, so that their extirpation is very difficult.

Adenoma Malignum. This may occur in young subjects. It forms a rather bulky

tumor that replaces the thyroid lobes, and it resembles the parenchymatous form of fetal adenoma microscopically, except that its small acini are incomplete. Instead of each acinus having a separate and complete wall of cuboidal epithelium, two or more acini share part of their wall, and a "party wall" composed of a single layer of epithelium, instead of two layers, separates their



Field from "adenoma malignum," a questionably malignant form of fetal adenoma of thyroid. Note "party walls" shared by adjacent acini. Each acinus should, instead, be surrounded by a complete ring of epithelium.

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Papillary Adenocarcinoma. This is the malignant form of the papillary cystadenoma of lateral thyroid origin, from which it differs in its less differentiated appearance, its more luxuriant growth, the large number of mitoses it reveals, and its tendency to invade neighboring tissue other than the lymph nodes, notably the sternocleidomastoid muscle. These tumors tend to recur after removal, and if early removal has

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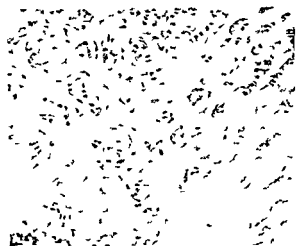
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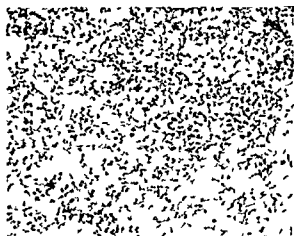
the thyroid. They are not readily identified unless one has had considerable experience with them. They are firm, yellow, and only a few millimeters in diameter, and bits of fat, small lymph nodes, and small lobules of aberrant thyroid tissue may all be readily mistaken for them by both surgeon and pathologist. They may be congenitally absent or very small, or (like those of the dog) they may be scattered as islets embedded in the thyroid.

Low levels of calcium in the blood in the course of rickets, long standing renal insufficiency, and disturbances in the absorption and metabolism of inorganic calcium salts may all cause hyperplasia of the parathyroid glands. A combined weight of these exceeding 130 mg is indicative of hyperplasia. In such cases nothing is noted on gross examination save that the organs are enlarged. Microscopically, however, the clear cells begin to appear among the chief cells, the latter being more granular than the former. Oxyphil cells, which Castleman and Mallory consider as possible degenerated forms, may also increase in number, normally they are found only as scattered examples. These authors have translated the German term "Wasserhelle Zellen" literally as "water clear cells", as a term for general use "limpid cells" or more simply "clear cells" would seem to be less cumbersome.

There is considerable bearing of the physiology of these organs upon the surgical pathology of at least two systems in the body—the skeletal and the urinary. Lack of parathyroid substance ("parathormone") causes tetany, while rapid removal of all parathyroid tissue can result in rapid death. In the case of hyperplasia per se, or when this is connected with the presence of adenomas of the glands, osteitis fibrosa cystica (von Recklinghausen's disease of bone) and renal calculi may be noted. Thus far no connection has been established between such changes and Paget's disease of bone. In hyperparathyroidism the serum calcium level is high and the phosphate low, and

calcium is withdrawn from the bones and excreted in the urine, in hypoparathyroidism the reverse is true and tetany results without any bony changes being occasioned.

Tumors. These are usually well encapsulated and lobular, and although they usually weigh in the vicinity of 5 to 10 Gm weights of 68 Gm have been recorded. As the weight of one hyperplastic gland is about 3 Gm, and as the adenomas develop,

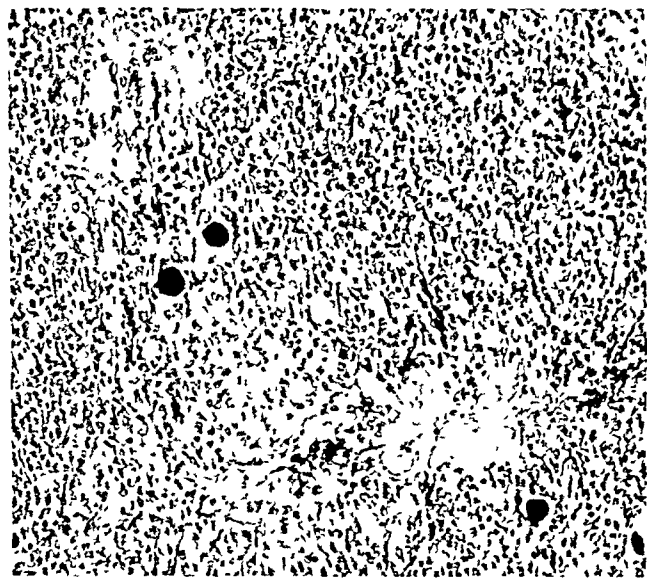


Chief cell adenoma of parathyroid, composed of small chief cells that tend, here and there, to approach the "limpid" or "water clear" type

as a rule, from one parathyroid, this is much more formidable than it would appear at first glance.

ADENOMA. As Castleman and Mallory have noted, there are four types of cell that may produce tumors—the chief cell, the clear cell, the pale cell, and the dark oxyphil cells. Up to the age of puberty the chief cells are the unique constituents, after this pale oxyphil cells begin to appear in groups, at the age of 50 they form large islands. The dark oxyphil cells are in a decided minority, lying here and there in the neighborhood of the stroma. Adenomas composed of chief cells are by far the most numerous, next come transitional clear-celled tumors, then glandular and cystic forms, and finally neoplasms composed of transitional oxyphil cells. In a series of 137 cases collected from the literature 59 were

cells lining elongated spaces and completely packing them. There is one type that closely resembles a lymphosarcoma and was often mistaken for it until Ewing called attention to the fact that it was a small-celled variety of carcinoma. Its cells have more



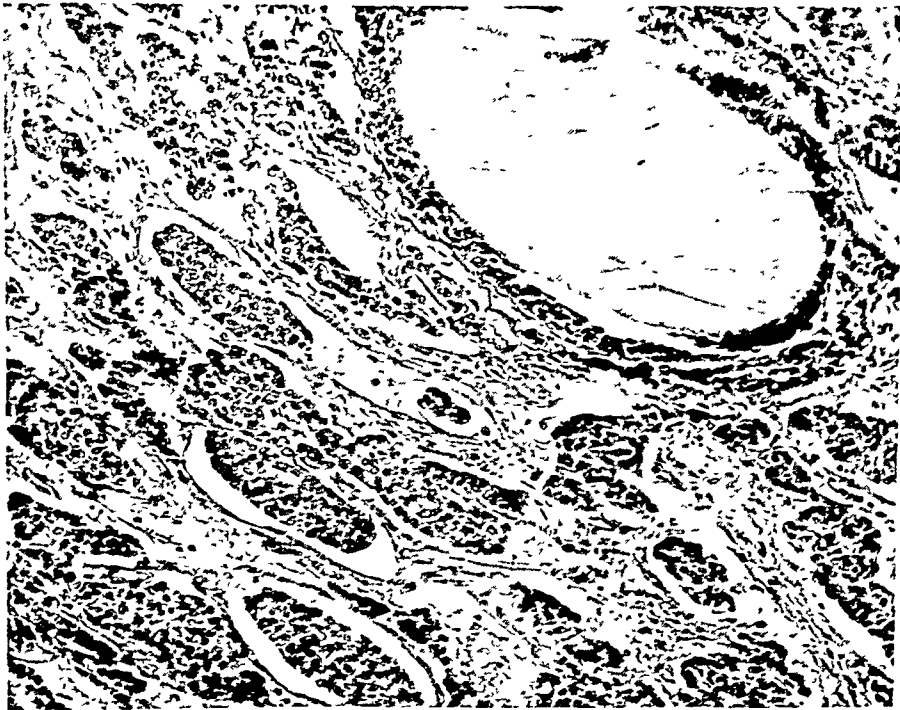
Carcinoma of thyroid, intermediate between small-celled type and adenocarcinoma. Black masses are inspissated colloid secreted by cells of tumor.

cytoplasm than do the lymphocytes. This type is polygonally outlined, and the cells tend to be lined up into short chains suggesting an epithelial arrangement. Silver impregnation reveals a reticulum that is typical of epithelial stroma and does not run all among the cells like that of the lymphoid tissue. Its cells may invade the large veins in the thyroid and thus carry the growth to the skull, sternum, spine, ribs, and long bones.

It is easy to be misled by the appearance of these thyroid carcinomas; some of them exhibit good differentiation and are very malignant, while some that have a more bizarre appearance may be less so. One can make no definite prognosis and should be guided by evidence of invasion of the thyroid veins; Graham insists upon finding this before making a definite diagnosis of malignant neoplasm.

PARATHYROID GLANDS

There are usually four of these little glands: one tucked away near each pole of



Small-celled carcinoma of thyroid showing replacement of epithelium in some acini by small lymphocytoid cells that might readily pass for those of lymphocytic lymphosarcoma were it not for their arrangement and their obvious connection with epithelium of thyroid gland.

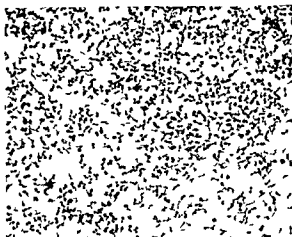
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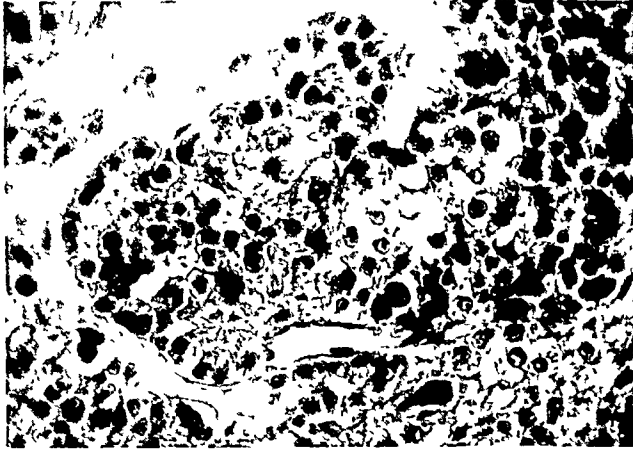
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SUPRARENAL GLANDS

These glands of internal secretion develop in the neighborhood of the mesonephros and hence of the wolffian body. For this reason there are opportunities for a "shuffling" of suprarenal tissue into the kidneys, where it is readily identified, or into the testes or ovaries, where tumors that have a distinctly suprarenal appearance have been noted. Hence there has been a great deal of theorizing and conjecture concerning such neoplasms. Otherwise the developmental anomalies and regressive changes in the suprarenals are of little surgical pathologic importance.

As surgeons sometimes take biopsies from the suprarenals it is well for the pathologist to have various lesions in mind, although they belong more properly in the realm of general pathology. The organ may exhibit a progressive atrophy in the true form of Addison's disease; it may be the site of extensive hemorrhage in connection with acute infectious diseases; and in childhood massive hemorrhage gives rise to the Waterhouse-Friederichsen syndrome, in which there is sudden onset of fever, headache, vomiting, diarrhea, and abdominal pain in infants and children who were apparently well up to the time of the sudden onset of the attack. Should such a patient be laparotomized the chief finding would be massive hemorrhage in the suprarenals which might destroy their entire substance and convert them into mere sacs of blood and clots. Tuberculosis frequently destroys one or both suprarenals, converting them into caseous masses.

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ilar adenomas may occasionally be displaced into the medulla

When a cortical adenoma is of considerable size it effects characteristic changes in the host. Sexual changes may be noted in childhood or young adulthood, in boys there is precocious development and maturation of the genitalia, even accompanied by seminal emission in patients much too young to be capable thereof under normal circumstances. In girls there is acne, and changes in the bony skeleton may be observed.

In adult women the changes are much more striking, there is a development of virilism with an extraordinary assumption of the masculine habitus: narrowed hips, flat chest, and breasts like those of a man, with small nipples and little substance. The growth of hair on the body becomes that of the male: there is facial hirsutism, a masculine pubic scutum that extends up the midline of the belly, and the development of a hairy chest. The voice becomes low pitched and hoarse. The clitoris becomes enlarged and there is amenorrhea. In men, however, there are loss of pubic and axillary hair, impotence, and atrophy of the external genitalia. The changes in women are similar to those noted in Cushing's syndrome in connection with basophilic adenoma of the pituitary, in which small cortical adenomas of the suprarenals are a fairly regular concomitant, but they differ in some notable particulars. There is no adiposity of the face to produce the typical "moon" or "pig face," while there is hypertrophy of the clitoris, which is absent in Cushing's syndrome.

The functional tumors are firm, gray, and nodular and may attain diameters of 8 to 12 cm., they are ovoid and well encapsulated. Microscopically there is a close resemblance of their histology to that of the cortex, this is so readily recognizable that they need no further description.

MALIGNANT CORTICAL ADENOMA This is a rare tumor that is soft and brownish yellow, it may grow to great size. Its micro-

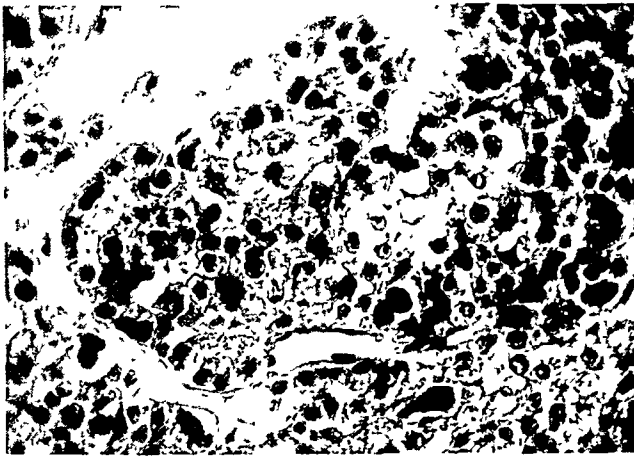
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MEDULLARY TUMORS As the suprarenal medulla is composed of nervous elements and only a few typical epithelial ones, the tumors that stem from this part of the gland are necessarily largely of the nervous type that will be discussed with the pathology of the nervous system, these are notably the sympathicoblastoma (sympathoblastoma) and the pheochromocytoma and pheochromoblastoma. Patients suffering from the sympathoblastomas present no characteristic symptoms, being literally overwhelmed by the tumors and their metastases. Those harboring the medullary tumors, however, exhibit paroxysmal hypertension and other symptoms referable to oversecretion of epinephrin.

The medullary tumors are usually of small size, although larger ones that do not exceed 10 cm. may occasionally be found. The histology of this sort of tumor is variable. There are a great many anastomatic, multipolar cells arranged in a haphazard manner or lined up around acinar spaces in a gland like manner. They show a light yellowish brown pigment which aids in the diagnosis. Silver impregnations may reveal that a tumor from the suprarenal medulla which resembles a carcinoma in ordinary hematoxylin and eosin stains is in reality composed of multipolar cells that appear to lie within spaces almost like membranous sacs. It is not always easy to determine whether or not these tumors are malignant if they exhibit pleomorphism and mitotic figures they should be regarded as malignant. The cells may be aligned along the outside of capillaries, much as are the astro-

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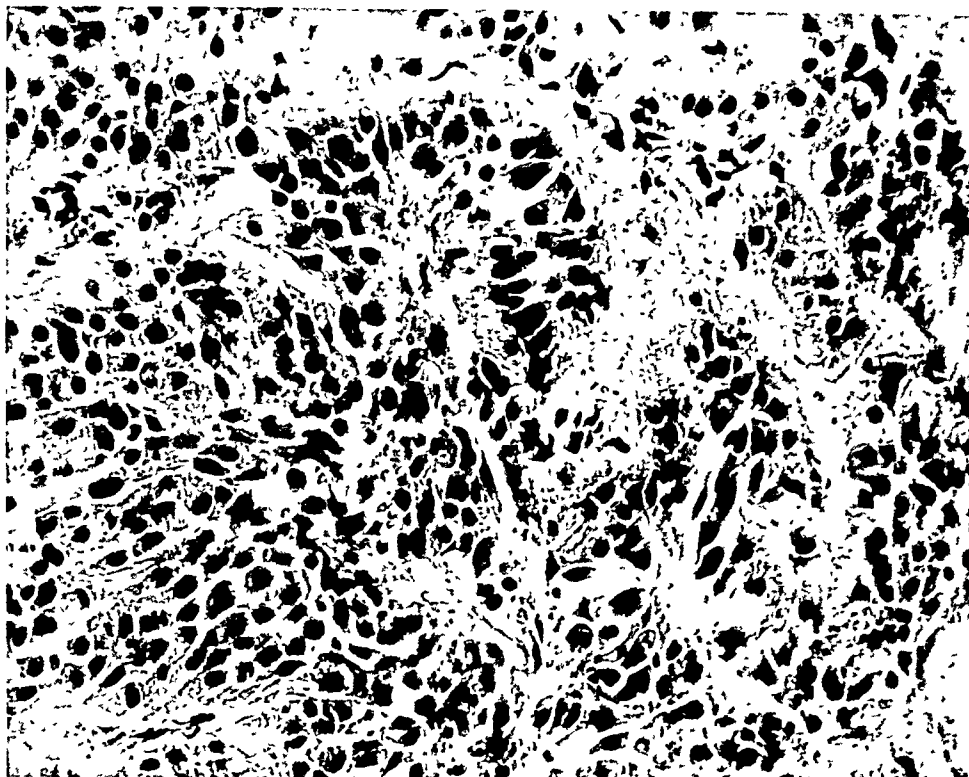
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Pheochromoblastoma from medulla of suprarenal gland. The patient exhibited paroxysmal hypertension. Histology of this tumor has little resemblance to that of suprarenal medulla. (Army Medical Museum 65551.)

cytes of a glioma, and there is much to indicate that there is kinship between these central gliomas and the suprarenal tumors which might be considered as peripheral gliomas. Furthermore, they have been observed in patients suffering from neurofibromatosis and multiple-pigmented areas in the skin, which further enhances this possibility, as gliomas are also common in that disease and may determine its fatal outcome. Tumors of a very similar type and appearance may be found at some distance from the suprarenal, but not so far away that they could not be explained upon the basis of displaced suprarenal tissue.

“HYPERNEPHROMA.” This malignant tumor has been discussed with the pathology of the kidney. Since it was described by von Grawitz it has been considered to be derived from displaced suprarenal tissue in the kidney or from alterations in the renal tubules. Ewing recognizes a hypernephroma and a clear-celled carcinoma of the kidney that differ only in so far as the former grows in solid alveolar masses while the



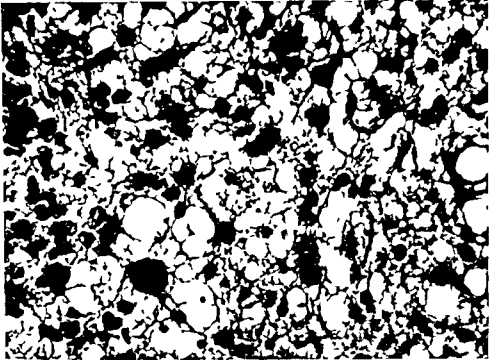
Field from pheochromoblastoma shown in preceding illustration; here it presents numerous cells heavily laden with melanin. (Col. F. H. Foucar.)

latter produces tubules, acini, and papillary overgrowth. The evidence on both sides of the question of origin of these tumors is very strong—so much so that it is difficult to decide which to espouse, one makes up one's mind to take one view and is then confronted by evidence that appears to be decisively in favor of the other.

Therefore it can be said that the four neoplastic types may be arrayed into two clinical groups, one functional and the other not. The question is far from being settled.

CAROTID BODIES

These small glands, like many other organs of internal secretion, are of surgical

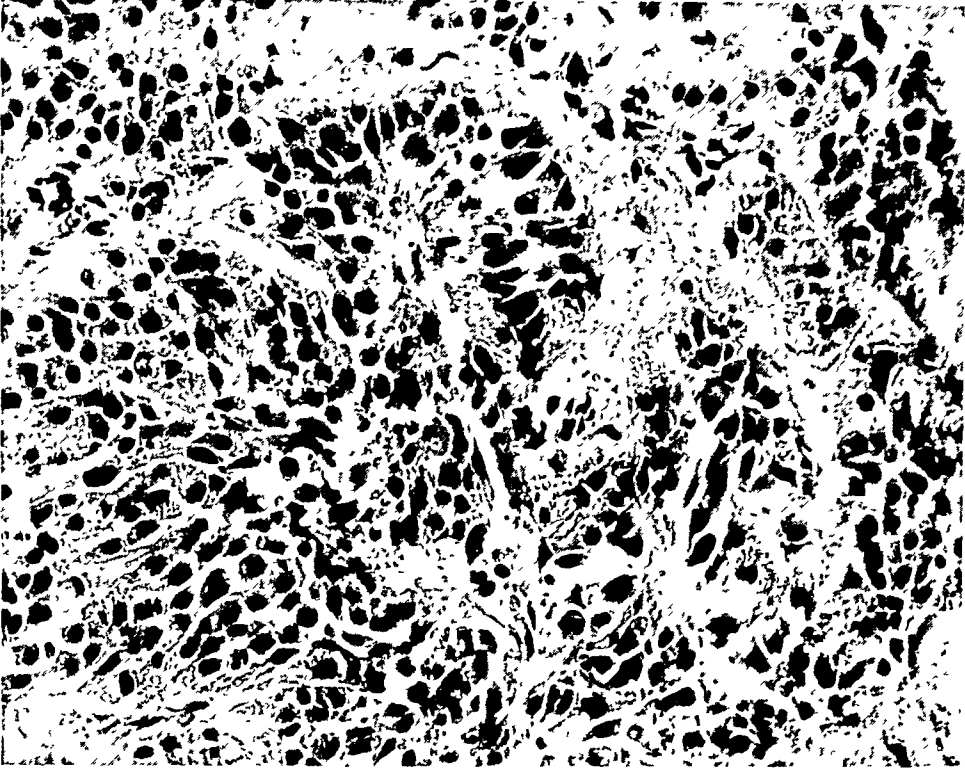


Silver impregnation of a pararenal tumor, probably of suprarenal medullary origin. Note resemblance of its cells to those of glioblastoma multiforme. Ordinary stains fail entirely to demonstrate these "spider cells."

Morphologically speaking, there are several sorts of tumor that are composed of large clear cells and resemble one another so closely that decision as to any diagnostic differences between them is impossible. The tumors of the suprarenal cortex, the "hypernephroid tumors" of the ovary, the clear celled carcinoma of the kidney and the hypernephroma of that organ are practically indistinguishable under the microscope. The suprarenal cortical tumor and that of the ovary both produce virilizing changes in women, clear celled carcinoma and hypernephroma produce no symptoms other than those of any malignant tumor: growth, metastasis and a fatal outcome if untreated.

pathologic importance only when they produce tumors. Their size is small and they are situated at or near the bifurcation of the carotid arteries. Microscopically they are seen to be made up of masses of chromaffin cells (which have an affinity for chromium salts and for silver) that lie in irregular alveoli around which courses a network of small vessels. Apposed to these and between them and the masses of chief cells are larger, stellate cells that are closely applied to their outer surface and readily escape observation.

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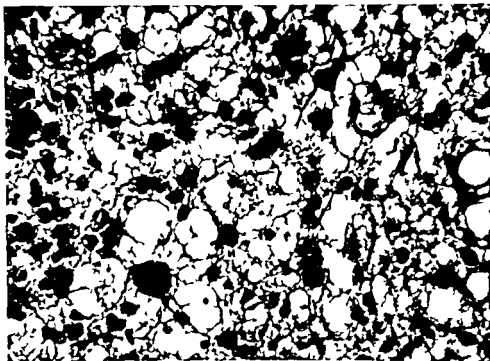
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uated at the site of the gland, which is usually overshadowed by the tumor and lost to sight; it is very apt to encircle the carotid vessels and cause interference with the circulation. It may grow to considerable size and form a leathery growth which is firmly welded to the vessels that it encloses, so that in order to remove the tumor the ves-

tion. The microscopic picture, however, is very disorderly and deviates widely from that of the normal gland. The cells are large and pleomorphic, mitoses abound, and the grouping of the elements is very variable and somewhat suggestive of that of a retothelial sarcoma on account of the anastomotic network of cellular processes that is



Carcinoma of carotid body. When the large, paler cells seen in this figure predominate, the tumor takes on the "peritheliomatous" type.

sels must be resected. Histologically it imitates the architecture of the normal gland very closely, merely presenting as an exaggerated carotid body. It gives rise to no striking symptoms, and usually it is better to leave the growth alone than to face the hazards of working so intimately about the wall of the carotid vessels.

CANCEROUS GROUP. Chief-cell Type. This tumor resembles the adenoma grossly; it also shows a fairly regular architecture under the microscope, but the alveolar masses become distorted, often being very irregular in size and shape, and their cells reveal mitoses without exhibiting many signs of metaplasia.

Peritheliomatous Type. In this the larger stellate cells proliferate about the vessels, and because of this the tumor has been known as a "perithelioma" in the past. Very little can be determined from gross inspec-

set up. The growth tends to necrose rather rapidly, as it interferes with the vascular supply of the tissue.

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17

Male Reproductive System

TESTES (INCLUDING SCROTUM)

CONGENITAL ANOMALIES
SEROUS AND VASCULAR LESIONS OF SCROTUM
TESTICULAR BIOPSY
INFLAMMATION
TUMORS OF EPIDIDYMIS
TUMORS OF TESTIS

SEMINAL VESICLES

PROSTATE
RETROGRESSIVE CHANGES
INFLAMMATION
NODULAR HYPERPLASIA
TUMORS

Development This system * is developed from the wolffian duct, a derivative of the mesonephros. After the testis and its appendages have been formed they gravitate to the scrotum via the lumbar gutters and the inguinal canals, guided by cords that are known as "gubernacula testis." It must be remembered that this migration from the region of the kidney to the scrotum is not as formidable in a small embryo as it would be in an adult, and the distance travelled by these organs is therefore far shorter than one might at first think.

TESTES

Congenital Anomalies **UNDESCENDED TESTIS** The only congenital anomaly of the testis that is of much importance to the surgical pathologist is that of "undescended testis" or (if it is bilateral) cryptorchidism. In both instances the testes develop as usual in the neighborhood of the kidney, but fail to follow the gubernacula all the way to the scrotum, hence they may be found at any point between the kidneys and the external inguinal rings. The most usual sites are the lumbar region, the internal inguinal ring, the inguinal canal, and the external ring. The commonest of these is the site within the canal. The cause of

this lack of complete descent is a matter of speculation as to adhesions about the testis, lack of pull on the part of the gubernaculum, and similar factors.

As the organ or organs are ectopic, and as they may be in the inguinal canal, they are readily subjected to trauma by blows or muscular contraction. They are more likely to become strangulated by torsion of the cord, and it is asserted that they are more liable to develop malignant tumors than are normal, fully descended organs. The atrophy that often occurs in an ectopic testis may be a part of its failure to develop properly. Although such testes may manufacture spermatozoa up to the 25th year or thereabouts, they then undergo marked atrophy and fibrosis.

It is unusual to find an undescended testicle that does not show these phenomena, possibly most patients wait too long before seeking medical advice.

Microscopically, one notes a very simple picture in which the cells of the tubuli contorti are very much alike, they are large, pale, and primitive without showing mitotic activity. They surround the lumina of the tubules in only two or more rows, instead of several, and it is difficult to distinguish between the Sertoli and the functional cells or spermatogonia which fail to mature. The interstitial glands, composed

* The pathology of the penis is considered under the urinary system for reasons stated in that section.

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PARATHYROID GLANDS

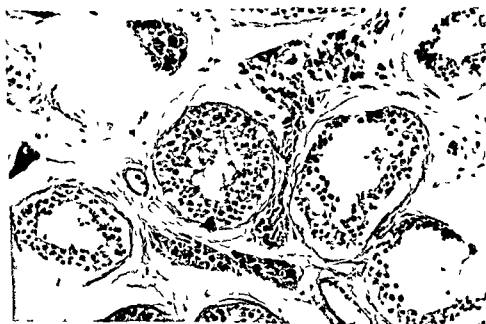
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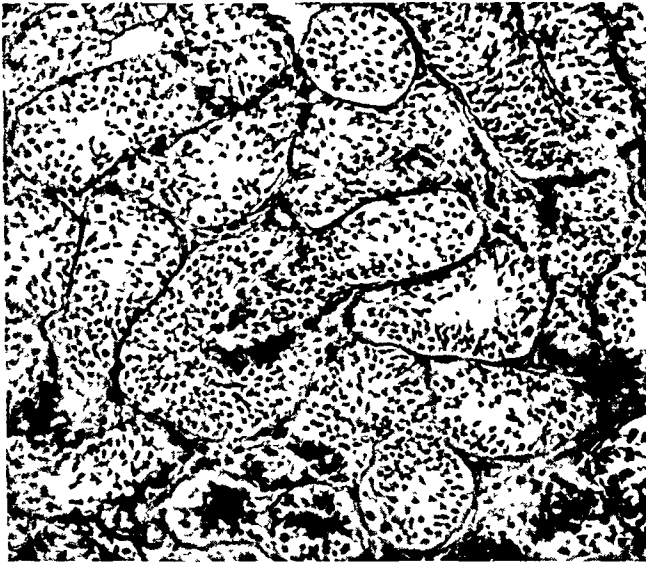


Section from testis of old man castrated in connection with treatment of prostatic cancer. It shows complete atrophy and advanced fibrosis. Gray rings are fibrous walls of tubuli contorti.



Field from senescent testis of 72 year old man. Note thinned-out lining of tubuli contorti and large and prominent interstitial glands of Leydig composed of large, polyhedral elements.

of Leydig cells, are, on the contrary, increased in size, as is usual in conditions affecting the functional activity of these organs, as in the eunuchoid type of hypopituitarism. Fibrosis may be very marked, and the gland may be largely replaced by soft and edematous connective tissue. Failure of descent of the testis is frequently associated with the developmental anom-



Section from typical cryptorchid or undescended testicle. Note juvenile type of epithelium and complete lack of differentiation of spermatogonia in these contorted tubules.

alies that lead to hermaphroditism or pseudohermaphroditism—conditions that do not concern us here.

SCROTUM

Serous and Vascular Lesions. **HYDROCELE** has been discussed under Acute Serositis in the chapter on Serous Membranes. **VARICOCELE** is merely a localized state of varicosities in the pampiniform venous plexus.

ELEPHANTIASIS. Prolonged lymph stasis of the scrotum may follow interference with the drainage of this structure, whether from cicatricial contractions, excision of lymph nodes, or, most commonly (if the matter is considered internationally), obstruction to the lymphatics by the adult worms of *Filaria bancrofti*. In this disease the scrotum may attain enormous size, not infre-

quently becoming so large in the case of African Negroes that it reaches to the ground, upon which it drags and becomes excoriated. Microscopic examination of specimens will show marked lymphatic stasis and dilatation of the lymphatic channels; the filaria may be found in these at the point of obstruction, and their larvae may be demonstrable in the circulating blood.

TESTIS PROPER

Testicular Biopsy. Before the lesions of the testis are described it would be well to discuss the matter of testicular biopsies, which are a valuable adjunct to the diagnosis of sterility in the male. They afford an idea of the histology of the testis, which cannot be determined by examinations of semen alone, and the mechanism of spermatogenesis in a particular patient may thus be checked over in order to determine whether or not the fault is irreparable (as in complete atrophy) or amenable to hormonal therapy (as in the case of failure of maturation of the spermatids). The biopsy is readily carried out under local anesthesia and presents no hazards at all. The testis is exposed through a small incision and a small bit of parenchyma is removed through the tunica; fragments with a diameter of 2 to 3 mm. are large enough to work with. They are immediately fixed in Bouin's solution or alcohol-formalin and are run through the usual process of sectioning.

Microscopic examination shows the normal gland to be active and the spermatogonia to be dividing and producing prespermatids and spermatids, while the interstitial glands are of the normal, unobtrusive appearance. The smaller spermatogonia and prespermatids, with the spermatozoa, usually form island-like masses in the lumina of the contorted tubules; in the sterile testis this is not the case. The tubules may be entirely atrophic (as described under "undescended testis") and the stroma fibrous, or it may be found that the process

testis and epididymis that are riddled with acute purulent foci of inflammation that may involve the neighboring scrotum as well

INFECTIOUS GRANULOMA Tuberculosis This is essentially a disease of the epididymis, where it begins in the globus minor and spreads, eventually invading the testicular tissue and extending through the tunica



Subacute epididymitis showing an abscess (lower left), four vasa efferentia, and background of fibrotic and inflamed tissue

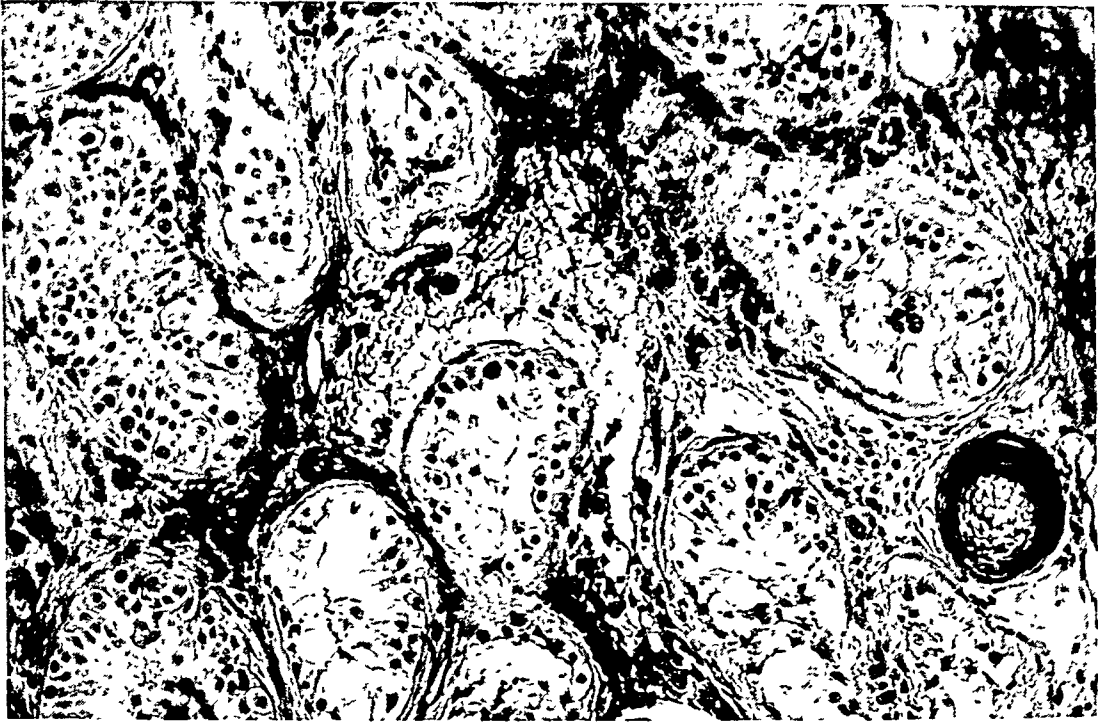
to the scrotal sac. The testis is invaded by direct extension of the process through the rete. From the testis and epididymis the infection may ascend along the cord to the seminal vesicles and the prostate. The disease is seldom observed in its early stages in the surgical laboratory, where the specimens usually show advanced caseous tuberculosis with destruction of all or part of the testis and a riddling of the epididymis with tubercles. Mixed infection is not uncommon.

Syphilis While tuberculosis usually affects the epididymis first, syphilis attacks the testis and seldom involves its appendage. Although a diffuse fibrous type is described, surgical specimens of luetic orchitis usually exhibit one or more gummata which do not differ from tertiary lesions in general.

Tumors of Epididymis Tumors of the epididymis are uncommon. Cysts or the hydatids of Morgagni are of no importance. A wide variety of lipomas, fibromas, myxomas, leiomyomas, and adenomas have been described, but for practical purposes they exist in the literature of pathology rather than in its practice. Two tumors seem worthy of special consideration, one of these apparently arises in the vascular endothelium, the other is a carcinoma of the vasa efferentia.

"ANGIOSARCOMA" This tumor has been seen in our practice on three occasions in a long series of epididymides, mostly tuberculous, which showed no tumor. It is a stone-hard, spherical growth that usually lies near the junction of the epididymis with the cord, up which the growth may extend a short distance. On gross examination it is light brown, almost ligneous in consistence and rather moist and homogeneous on section. On account of this stony consistence it usually arouses suspicion of carcinoma in the mind of the surgeon.

Its microscopic appearance at once presents problems of interpretation. It is chiefly composed of dense desmoid tissue in which are embedded channels of irregular and geographic outline lined by atypical cells which tend to bulge into the lumina like those of vascular endothelium, than which, however, they are larger and more hyperchromatic. The channels may contain blood, coagulated material resembling lymph, or nothing demonstrable. Careful study of the tumors reveals occasional mitotic figures, and the channels lie in positions that one might ascribe to lymphatics or blood vessels. On account of the atypia of the cells and the presence of mitotic figures the growth usually goes under the name of "angiosarcoma." However, there is a possibility that the channels may represent vestiges of the wolffian duct which might be connected with the rete. The tumors appear to be at least histologically malignant, although those that we have studied did not recur after



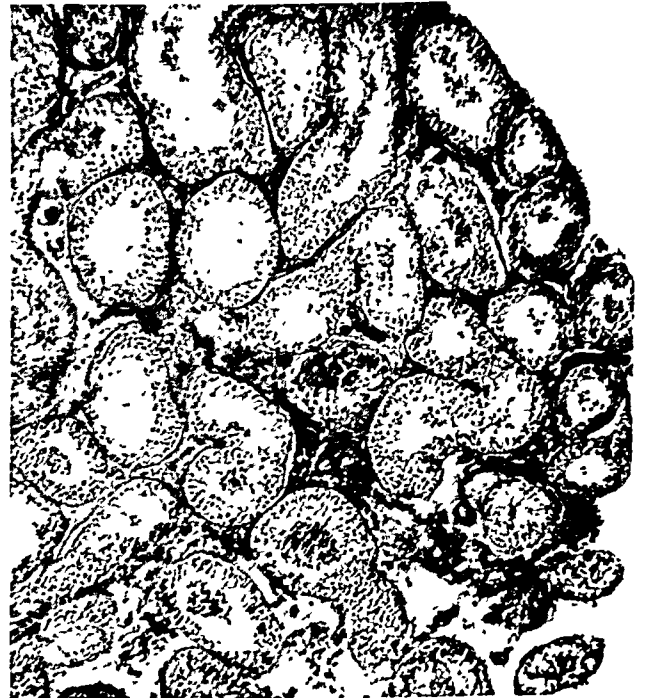
Biopsy showing complete azoospermia. Spermatogonia are poorly differentiated and comparatively inactive; differentiation scarcely proceeds as far as formation of prespermatids. No spermatozoa are produced.

of spermatogenesis shows arrest at some point in its course. This may often be at the stage of maturation into prespermatids, which appear to be normal but fail to develop middle pieces and tails. Or one may find very few spermatozoa of a mature type, usually lying at the periphery of a somewhat patulous lumen.

When no spermatozoa can be found, the diagnosis is aspermia, or aspermogenesis; when there is faulty maturation and a few mature forms may be observed, one speaks of "oligospermia." The prognosis in the former is usually poor; in the latter hormonal treatment with androgen may restore to the gland the ability to produce mature sperm. If the biopsies are found to be normal in every respect, the fault is to be sought elsewhere and may prove to be attributable to occlusion of the vasa efferentia or some similar mechanical reason. Sperm is stored in the epididymis, where its cells develop motility; sometimes the fault is here.

Inflammatory Lesions. ORCHITIS AND EPIDIDYMITIS. These most usually accompany gonorrheal infection, although they

may be caused by mumps or pyogenic cocci. Unless the infection results in the formation of an abscess it does not concern us. Occasionally one receives specimens of the



Biopsy showing typical picture of oligospermia; the spermatogonia are well differentiated, but very few spermatozoa are being produced, as differentiation halts before they are formed.

TERATOID TUMORS The practice of calling all such tumors of mixed lineage "teratomas" has given rise to great confusion, particularly among those who are not very familiar with the niceties of histopathology. It would seem better arbitrarily to reserve the term "teratoma" for the well differentiated, nonmalignant neoplastic monstrosities that show so many forms of tissue in their make up that Oberling has likened them to the offspring of a scrambled egg in his book, "Le Probleme du Cancer" (Unfortunately this happy simile does not appear in the English translation). Having limited the category of teratoma to these well differentiated and nonmalignant tumors, we may next consider the more primitive and malignant varieties as "dysgerminomas," which may be divided into three general subtypes

TERATOMA This tumor may be very well organized, almost resembling an embryo and suggesting parthenogenetic origin. The very well organized examples are sometimes known as "embryomas." How this type of tumor originates, however, is anybody's guess. It shows an organoid arrangement of tissues that strongly suggests the cephalic extremity of an embryo, this characteristic is common to teratomas both of the testis and of the ovary. Scalp, hair, bone, cartilage, teeth, and cerebral tissue are easily recognized, other duct like or gland like structures imitate primitive intestine, mammary gland, and other internal organs, but these more diversified types are relatively uncommon. Teratomas may be less well organized, the cellular elements being less readily recognized and scattered about in a rather haphazard fashion. The danger in a teratoma is the possibility of one or another group of cells being completely differentiated and thus constituting a malignant element that may spread through the tumor and metastasize, so that this sort of growth will show malignant and nonmalignant elements at one and the same time.

DYSGERMINOMA The entirely malignant embryonal tumors of the testis may be di-

vided into three groups: seminoma, embryonal carcinoma, and choriocarcinoma. The reader must remember, however, that



Teratoid form of testicular dysgerminoma which might equally well be called "malignant teratoma." It is slightly organoid but poorly differentiated. Several types of epithelium present in the field.



Dysgerminoma of testis of seminomatous type exhibiting a scanty lymphoid stroma. This is the best differentiated of the testicular dysgerminomas.

although the pathologist makes the classifications. Nature is quite indifferent as to his efforts in that direction, so that tumors crop up once in a while that are difficult to fit into any given category.

Seminoma The commonest of the dysgerminomas, this tumor grows rapidly, is

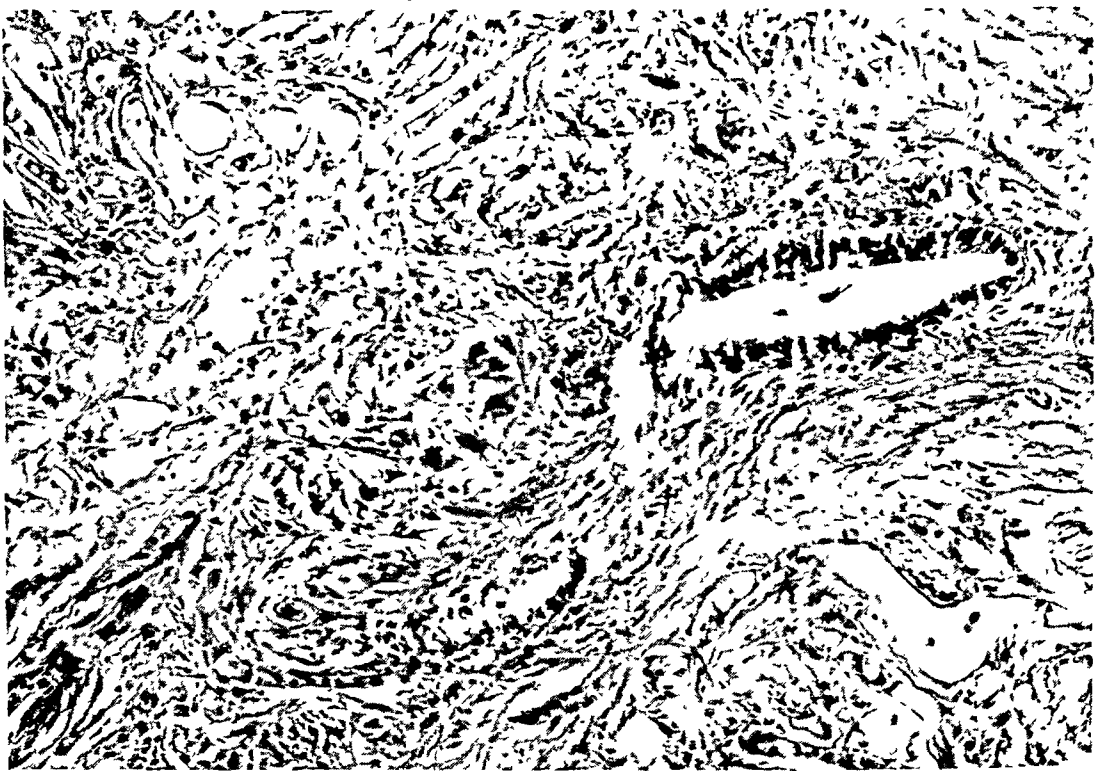
local removal, nor did they give rise to metastases.

Similar tumors in women have been described recently. In these cases they occur in the round ligaments.

CARCINOMA. Carcinoma undoubtedly develops in the tubules of the epididymis and rete testis; in both instances, firm to stone-

laboratory, but a section of one was recently submitted from another city in consultation. Since they are so rare, nothing can be said about the best course of treatment.

Tumors of Testis. As this organ is composed chiefly of totipotential gonadal cells many of its tumors are of a diversified



“Lymphangioma” of lower spermatic cord, sometimes called “lymphangiosarcoma” because of its tendency toward recurrence. It may represent an epithelial tumor originating in rests from the wolffian body, as a similar tumor has been described in women.

hard tumors are found that show poor definition and fade into the surrounding tissue. The microscopic appearance of the tumors which arise in the epididymis is that of a cystadenocarcinoma composed of predominantly cylindrical cells that form cystic spaces of variable size. They are not prone to metastasize early, and they are decidedly uncommon. Even rarer are the carcinomas that arise in the rete testis and, to a certain degree, reproduce its structure; they are composed of small cuboidal epithelial cells that show moderately infiltrative tendencies and are prone to form small papillary projections into small cystic cavities. No example of such a tumor has come to our

teratomatous type, as might be expected. However, there is some fibrous tissue in the stroma which occasionally forms fibromas, and Chevassu has described adenomas composed of small cuboidal cells. These adenomas are extremely rare. Tumors resembling those of suprarenal origin may occur along the cord or along the course of testicular descent; at the New York Hospital one was observed that lay midway between the kidney and the inguinal region and caused symptoms of hypertension. Such growths possibly represent bits of detached suprarenal tissue that have been carried down from the mesoblastema by the testis during its descent to the scrotum.

Choriocarcinoma In the male this growth resembles that seen in the female uterus and vagina, and it acts in the same manner. It usually occurs as a small tumor in the testis and metastasizes widely throughout the body, particularly to the lungs and liver. The origin of the tumor in the female is fairly easy to postulate, as it supposedly arises in chorionic rests, particularly those of a hydatidiform mole, but in the case of the male it is entirely mysterious, and its connection with apparently nonmalignant and unrelated teratoid tumors in the testis which show metastases that are frankly choriocarcinomatous makes the mystery even deeper. Microscopically the growth exhibits the large pile cells of the chorionic villi, usually very bizarre and distorted, with large and hyperchromatic nuclei and prominent large nucleoli, around groups of these typical chorionic syncytia are found. Patients with these tumors have been known to present hypertrophy of the breasts with secretion of colostrum, and their urine is

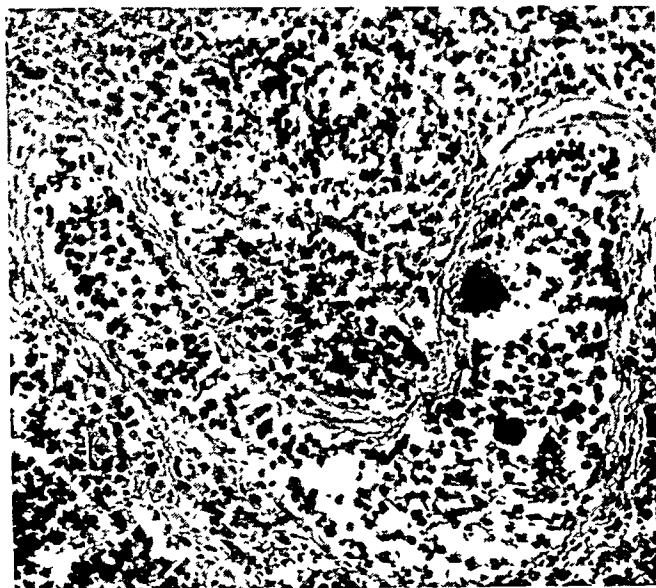


Intravascular metastasis of testicular dysgerminoma which shows characteristic appearance of choriocarcinoma although the primary tumor, removed several months prior to death was of the type of embryonal carcinoma (shown in another figure). This metastasis was found at autopsy near suprarenal.



Dysgerminoma of testis of chorionic type. Its cells are metaplastic and bizarre Langhans cells, but they are unaccompanied by any syncytia in this case. (Compare with metastatic choriocarcinoma shown above.)

soft, yellowish, and opaque, and has a distinct propensity for undergoing necrosis. It usually develops in the third or fourth

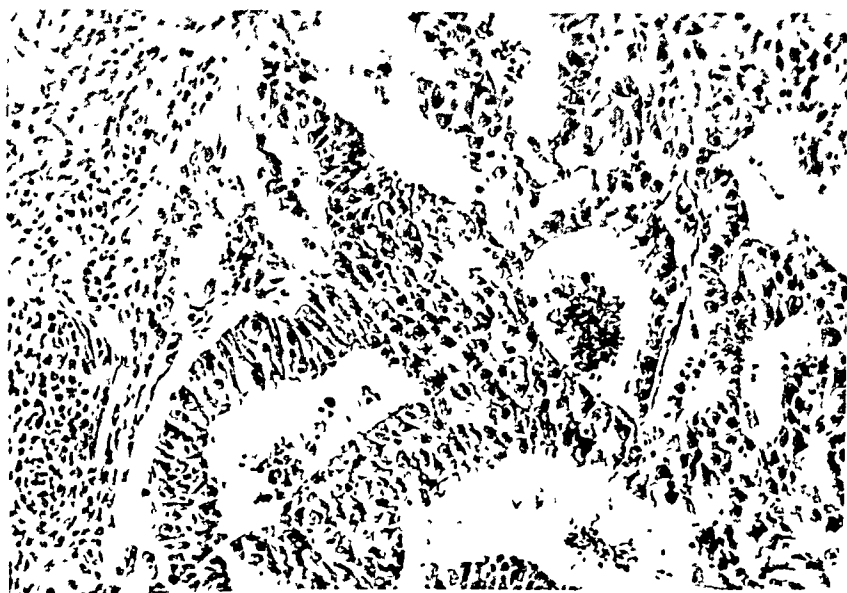


Characteristic field from dysgerminoma of type known as "seminoma" of testis. Foreign-body giant cells are sometimes found in these as well as in dysgerminomas of the female. There are two at right of figure.

decades. Its microscopic appearance may resemble that of the testis, with an alveolar arrangement of large cells that tend to grow smaller toward the centers of the alveoli. In some tumors they may all be rather large, while in others the smaller variety

predominates. This neoplasm metastasizes early by spreading up the spermatic cord. It may be cured by prompt castration and high avulsion of the cord, but by the time it is recognized it may have invaded the pelvic lymphatics and nodes. X-irradiation has probably proved to be of value in conjunction with operation, as there seem to be more cures now than there were thirty years ago. That it should be used alone, however, is doubtful. Its value apparently lies in controlling the pelvic metastases.

Embryonal Carcinoma. This looks much like the seminoma in the gross, but it is quite different under the microscope. Its cells are much more vacuolated and tend to grow in anastomotic chains, or to produce duct-like structures. Between these cords there may or may not be a variably developed interstitium of lymphoid tissue; hence Ewing always spoke of it as "embryonal carcinoma with lymphoid stroma." These are much more malignant than the seminomas and show a definite tendency toward hemorrhage into the parenchyma of the more adenomatous types. Irradiation was at one time believed to be efficient, but this belief is waning; it should at least be used over the pelvic region, however, as in the case of seminoma.



Embryonal carcinomatous type of testicular dysgerminoma. Some of scattered lymphoid stroma of this tumor is visible at left of picture.

urethral mucosa, may safely be diagnosed as chronic prostatitis, as may a generalized lymphocytic infiltration of the stroma of a smallish gland that shows few or none of the landmarks of nodular hyperplasia.

TUBERCULOSIS This appears first in the periphery of the gland in the form of yellowish caseous foci that are secondary to tuberculosis elsewhere and may represent a spread from the epididymis (as already indi-

The condition (one can scarcely term it a "disease") has its most frequent incidence in the seventh decade, beginning to appear in men of 40 and increasing up to the 65th year, it is most active, therefore, in the period of presenility. Married men apparently suffer from it a little more frequently than the single, and the yellow race seems to have less of it than the white or black, but there is little variation in its incidence



Group of typical corpora amylacea in section from prostate
Their laminated structure is well demonstrated

cated) or may arise independently of genito-urinary tuberculosis, in which case they are to be regarded as hematogenously spread from some pulmonary or other tuberculous lesion. According to Moore, about one fifth of tuberculous infections arise by direct extension, the rest being hematogenous.

Nodular Hyperplasia of the Prostate Moore has proposed this name for the condition that is generally known as "benign prostatic hypertrophy," which is a poor term when considered as to its literal meaning. It has been customary to speak of "adenomatoid hyperplasia" in New York Hospital, but as Moore's paper will have wide circulation and as his conception of the nodular character of the hyperplasia is well founded, it would be best to accept his terminology here.

within the white group as considered by nationality.

Deming and Neumann describe the early lesions and call attention to the fact that the hyperplasia is primary not in the glands, but in the musculofibrous stroma of the prostate. They say "It is probable that the solid nodule produces some stimulating and proliferating effect upon the epithelium of the duct wall, causing the epithelium to invade the solid nodule and form glands within it. The fibromyomatous tissue is invaded and overgrown by a more rapidly growing duct and glandular tissue, with the result that the nodule in its later stages develops the appearance of an encapsulated glandular tumor."

Moore confirms this statement after painstakingly examining approximately 700

generally positive in the Aschheim-Zondek test. Owing to the small size of the primary tumor, it is often overlooked until extensive metastases have made operation a hopeless procedure.



Dysgerminoma of testis showing chorioid and glandular ("embryonal carcinomatous") types combined in one section.

TUMORS OF LEYDIG'S INTERSTITIAL GLANDS. These are extremely rare and usually comparatively small; the largest that Ewing could find reported was 9 x 6 x 6 cm. They are well encapsulated, rusty brown in color, and they reproduce the microscopic appearance of the interstitial testicular glands.

SEMINAL VESICLES

These glands figure very little in surgical pathology. We have mentioned that they are often the site of tuberculous infection, and they are often sent to the laboratory attached to a prostate that is the site of carcinoma for examination as to the presence of metastatic foci or direct spread of the tumor. If the prostate has been removed early in the course of development of cancer, the chances of finding uninvolved vesicles is good, but experience shows that an extensively invaded prostate will exhibit local spread to the vesicles.

PROSTATE

This gland, the bane of the elderly male, surrounds the posterior urethra. If it becomes the site of nodular hyperplasia it interferes with urination, often to a very great degree.

Retrogressive Changes. After middle life is reached the prostate begins to fill up with waxy bodies called "corpora amylacea" which can be seen only under the microscope and are found to be concentrically laminated and possibly calcified. They are apparently of little importance. Long bouts of prostatic inflammation may give rise to the formation of small brownish stones, which are usually about 2 mm. in size, although they may occasionally attain a diameter of about 1 cm. and resemble gallstones in appearance.

Inflammation. ACUTE PROSTATITIS. This is a condition that should never come under the purview of the surgical pathologist, as it is best treated by medical means. Although the infection may be hematogenous, or by spread from the intestinal flora (*B. coli*), it is usually spread from the urethra in gonorrheal urethritis. The colon bacillus and the staphylococcus come next in order as etiologic agents. The gland becomes swollen, hyperemic, and painful, and abscesses may form in its parenchyma. The microscopic appearance is that of acute inflammation with abscess formation.

CHRONIC PROSTATITIS. There is some question as to whether this condition is a result of several bouts of acute inflammation or whether it may not start and continue as a chronic process. Furthermore, one must always distinguish between chronic inflammation as such and the diffuse lymphocytic infiltration that commonly accompanies nodular hyperplasia. Both may constitute chronic prostatitis, but the latter is so usual that it is taken almost for granted. A recognizable concentration of chronic inflammation about the verumontanum, with slight papillary overgrowth of the epithelium and prominent glandular infoldings of the



Fibrotic area in nodular hyperplasia of prostate showing dilatation of acini and accumulation of secretion. Sometimes this picture predominates in nodular hyperplasia and the organ is unduly moist and oozes milky fluid on section of the gross specimen.



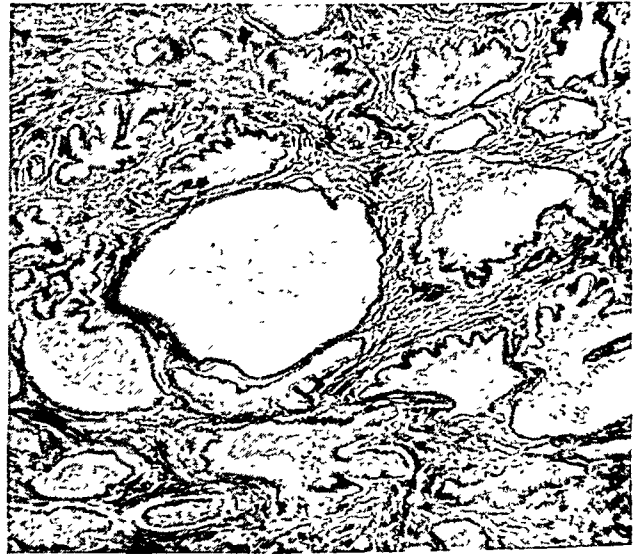
This illustrates a peculiar sarcomatoid change occasionally noted in musculature of prostates from elderly subjects. Picture is almost that of leiomyosarcoma, but patient shows no evidence that it is one. Four years after prostatectomy this patient died of cerebral apoplexy without further prostatic symptoms.

prostates in "step sections," in microscopic sections of the blocks from these serial gross sections. He believes that these nodules begin to form in the inner group of glands, which include those of the periurethral tissue and the acini anterior and mesial to the ducts of the lateral lobes. The middle prostatic lobe is less frequently the site of this hyperplasia, the anterior is rarely involved, and the posterior lobe appears to be almost entirely immune.

Moore postulates that glandular acini that develop from the stromal stimulation differ, in respect to their secretion, from normal acini. By the development of nodules, some of which show changes like those of intracanalicular mammary adenoma, the substance of the prostate is usurped by this new growth, which compresses the posterior lobe and grows inward and upward into the vesical lumen, where it may form the so-called "middle lobe," which assumes a globular shape and causes "ball-valve obstruction." Thus the new tissue is more like an abnormal hyperplasia of certain portions of the gland than it is like generalized hyperplasia or hypertrophy. According to Moore it affects those portions of the prostate secreting through ducts emptying cephalad to the verumontanum, while those that discharge distal to it do not undergo any similar change, but are more apt to exhibit regressive, senile involution.

The appearance of the nodules is characteristic: the epithelium is high columnar and forms true or pseudopapillae, as the case may be; these project into the lumina. The muscular tissue may show very bizarre, swollen, fusiform cells shaped like gourds and, by their size and appearance, suggesting sarcomatous change. These are commoner among subjects in the eighth and ninth decades. That this has any particular pathologic significance is not at all evident; very marked instances of such sarcomatoid stroma have been kept track of for several years without showing any signs of true sarcoma.

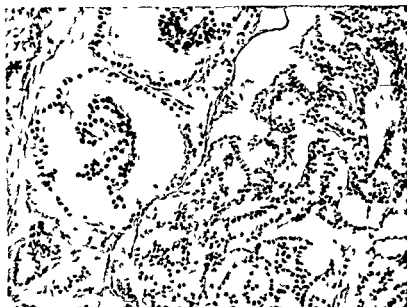
Moore calls attention to a peculiar phenomenon (also noted by Deming and Neumann) in the hyperplastic nodules: the epithelium lining the acini on the side directed toward the center of the nodule exhibits cylindrical hyperplasia, while that which lines the aspect directed away from that center and toward the periphery of the nodule is cuboidal. This disparity gives the acini



Typical nodular hyperplasia of prostate. Note that epithelium tends to be columnar on one side of acini, while it is flat and thinned out on opposite side (see text). There is moderate hyperplasia of musculo-fibrous stroma in this field.

a somewhat lopsided appearance that Moore likens to a shaded ellipse, one side of which has been drawn fine, the other heavily shaded.

Metaplasia of the ducts is a common stumbling block that causes many pathologists to diagnose a cancer that is not present. As carcinoma usually develops in the posterior lobe, and as this is seldom removed during ordinary enucleation (which is actually a lobectomy), it often happens that cancer appears in a prostate after enucleation and the pathologist is reproached for having "missed it." Moore points out that this is not necessarily the case, as a review of tissue removed prior to the development of cancer and reported as nod-



Adenomatous type of prostatic carcinoma which is prone to metastasize to bony skeleton



Massive multiacinar carcinoma of prostate This is a very malignant example

ular hyperplasia usually fails to demonstrate any neoplasm.

Tumors. ADENOMA. There is no doubt that an occasional adenoma may be found in the prostate—a small tumor that is sharply set off from the surrounding tissue and which, on microscopic examination, shows an adenomatous architecture without evidence of metaplasia. It resembles the nodule of nodular hyperplasia in a way, but it is more adenomatous, papillary, and epithelial, and much less stromal in its composition. Furthermore, it is apt to arise singly. Diagnosis of adenoma must be made with a certain degree of caution, and one must be sure that the structure is a true tumor and not a very hyperplastic area in a nodular hyperplasia. More importantly, one must rule out the small acinar form of adenocarcinoma, which often looks disarmingly like an adenoma.

LEIOMYOMA. Here again one must ascertain that a true, well-circumscribed tumor is present and that it shows only the characteristics of smooth muscle. Nodules of this tissue are often a part of nodular hyperplasia. Leiomyoma is not very common, only two having been seen in hundreds of prostates coming to our laboratory.

CARCINOMA. Ewing attributes this to nodular hyperplasia, but Moore concludes after statistical study that these conditions occur independently of one another, as we have just seen. The fact that the posterior lobe is the site of choice of carcinoma, while it is relatively unaffected by nodular hyperplasia, should have some significance. The seventh decade is the chief period of incidence, but carcinoma may be observed in the fifth. The gross appearance of a prostate that contains a cancer is not always characteristic, and it is often difficult to predict just what the microscope will show. The discovery on digital examination of the stony hardness of a carcinomatous prostate is more suggestive than its appearance to the naked eye. However, a well-developed carcinoma will be granular, whitish, and opaque and one may be able to discern

alveolar or acinar architecture. The tumor may invade the bladder and penetrate the capsule in the neighborhood of the seminal vesicles, which it then invades. This may occur early, but improved methods of diagnosis are enabling us to recognize cancer early enough to remove it before it has spread. Extension through the urethra to the bladder is sometimes noted.

Carcinomas metastasize along the rich lymphatic plexuses of the prostate and reach the prevertebral venous plexus, which may carry their cells far afield in the osseous skeleton without their traversing the portal system, liver, and lungs. Until Batson described this plexus, prostatic metastasis to the vertebral column without the involvement of the lungs and liver provoked much speculation. When it invades bone, prostatic carcinoma destroys the marrow and may show osteoplastic tendencies that, while the tumor is doing this destructive work, may produce bony trabeculae. That the epithelial cells are transformed into osteoblasts, however, is not proved; it seems highly unlikely. Meningiomas have the same osteoplastic ability.

Like other bone-destroying processes, metastatic carcinoma brings about changes in the blood that depend upon the presence of an acid phosphatase which, in this instance, is one normally found in the prostate but which is increased in the presence of carcinoma, possibly through androgenic activity. The presence of increased acid phosphatase of this type in the blood and urine of men suffering from prostatism is of great diagnostic value. The technic of determining these data belongs in the realm of clinical pathology.

The histologic types of prostatic carcinoma include adenocarcinoma, solid carcinoma, myosarcoma, and lymphosarcoma.

ADENOCARCINOMA. There are several types of this, but two general and typical forms will suffice for classification.

Multiacinar Form. This usually occurs in men in the fifth and sixth decades. It is composed of groups of irregularly cuboidal cells

come so highly dedifferentiated as to resemble a lymphosarcoma. It may also take on a scirrhous form with a marked desmoplastic reaction.



Area of tubular proliferation in prostatic carcinoma. Note closely set, deceptively well differentiated little ducts that compose this type of carcinoma.



Small-celled carcinoma of prostate which, despite its innocent appearance, is distinctly malignant.

MYOSARCOMA *Leiomyosarcoma* Leiomyosarcoma of the prostate is rare, but when it occurs it is no different from other tumors of that ilk as they appear in the uterus or intestinal tract.

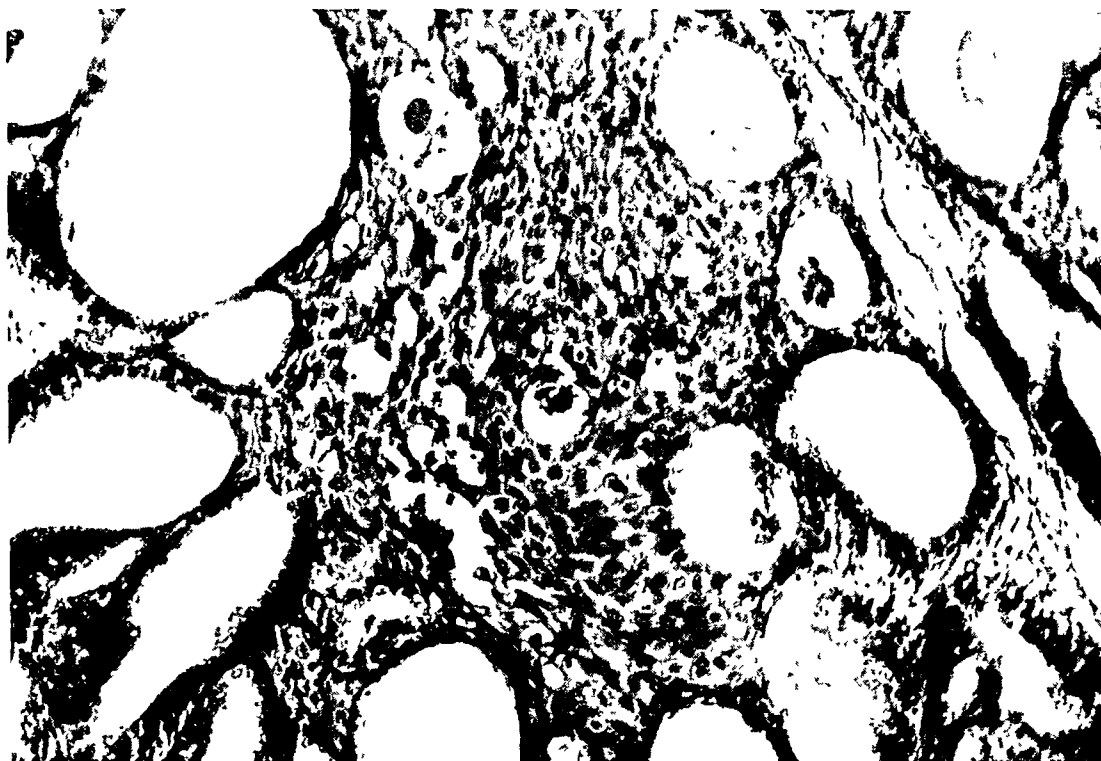
Rhabdomyosarcoma This is equally rare, only one case having been encountered in

twelve years in our laboratory. This tumor is usually noted in infants, the example referred to being observed in a boy of two years. The growth is somewhat analogous to those of the uterus and vagina, representing vestigial striated muscle in a smooth muscular organ. The cells may be disorderly and atypical or surprisingly well differentiated, with the appearance of a bundle of striated myofibrils and a single nucleus somewhere among them.

LYMPHOSARCOMA True lymphosarcoma of the prostate is very rare, as the organ has little association with lymph follicles. When lymphosarcomas occur they do not differ from those found in other situations.

ASPIRATION AND FROZEN SECTION BIOPSIES IN DIAGNOSIS OF PROSTATIC CARCINOMA A few words should be added concerning biopsies obtained with a large aspiration needle on a syringe (the needle being introduced into the prostate via the perineum). In the author's opinion the value of such biopsies is very slight. If the tumor is small and forms a small interior nodule in the gland it is almost sure to be missed; if the tumor is large and nodular the biopsy will prove that it is carcinomatous, but the surgeon knew that already and would explore it at any event. If, on the other hand, he does not wish to resort to operation and is anxious to confirm his impression the biopsy will be of positive value. Aspiration biopsies are successful when the explorer catches carcinomatous cells in his needle; otherwise they are quite valueless. A negative biopsy is likely to be misinterpreted and is positively misleading, as carcinoma may indeed be present, but have been missed by the needle.

It is preferable to stand by at a perineal dissection or a transurethral resection, obtain a good block of tissue, and examine this by frozen section. The perineal method will expose the prostate, the tumor may be seen and a generous biopsy specimen removed; the transurethral approach may readily miss carcinoma in the posterior lobe. A piling up of prostatic cells into small projections into



Prostatic carcinoma, showing unusual epidermoid metaplasia which is demonstrated at center of field.

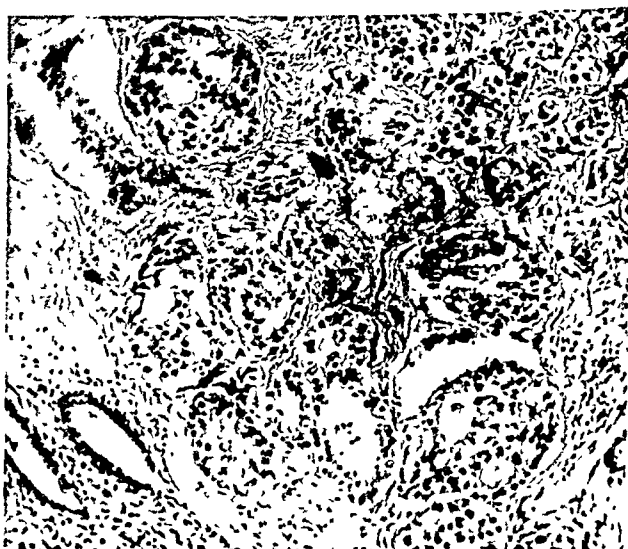
tending to form aggregations comprising several small acini that are clustered together within a normal acinar space in the stroma. This tumor looks mild and shows relatively little metaplasia and few mitoses, yet it carries a very poor prognosis, as it metastasizes early and widely.

Large Acinar Form. This, in contrast to the multiacinar type, is more often noted in older men in the seventh and eighth decades; it grows more slowly and is less prone to early metastasis. It is composed of large acini lined by columnar cells that may vaguely resemble intestinal epithelium.

Other Forms of Adenocarcinoma. One not infrequently finds a rather tubular or small-acinar form that may puzzle the observer by its fairly regular architecture; it may seem to be part of a simple hyperplastic process, but its component cells are abnormal. They may be vacuolated and clear or they may be compact and cuboidal, with hyperchromatic nuclei. An unusual variety is one recently observed in our laboratory which apparently arose in the utricular portion of the organ and, on microscopic examination, bore a marked resemblance to endo-

metrial tissue. Not only did the acini of the tumor resemble endometrial glands, but the stroma was the loose, fusicellular variety typical of endometrial stroma. This tumor (the only one we have seen) was very malignant and metastasized widely after invading the bladder en masse.

SOLID TYPE OF CARCINOMA. This may have a pseudoalveolar structure or it may be-



Typical field from multiacinar carcinoma of prostate. This is a malignant form that metastasizes early to the skeleton.

18

Female Reproductive System

VULVA

INFLAMMATION
TUMORS

VAGINA

TUMORS
CYSTS
EXAMINATION OF VAGINAL SMEARS
DESCRIPTION OF VAGINAL MUCOSA
VAGINAL SMEARS IN DIAGNOSIS OF CANCER

UTERUS AND CERVIX

INFLAMMATION (ENDOMETRITIS AND CERVICITIS)

TUMORS

PLACENTA

VASCULAR CHANGES
INFLAMMATION

PLACENTA (*Continued*)

HYDATIFORM MOLE

UTERINE CURETTINGS FOR DIAGNOSIS OF PREGNANCY

FALLOPIAN TUBES

INFLAMMATION (SALPINGITIS)
ENDOSALPINGOSIS
TUMORS
ECTOPIC PREGNANCY

OVARIES

CORPUS LUTEUM
INFLAMMATION
CYSTS
TUMORS
CLASSIFICATION
TREATMENT

VULVA

Congenital malformations of the vulva are of little surgical pathologic importance, as they present problems for the plastic surgeon who works with normal tissue.

Inflammations of the glands of Bartholin constitute the bulk of surgical specimens from this portion of the female genitalia. They may be infected as a sequela of vulvitis, whether pyogenic or gonococcal. After a few such inflammations, they may become obstructed with the formation of cysts having rather thick walls which are liberally supplied with glands composed of clear cylindrical cells like those of the nabothian glands of the cervix. The practice of some surgeons of filling the cyst with a low melting point paraffin in order to facilitate orientation while extirpating that structure should not confuse the pathologist, when he finds the lump of paraffin it will be readily explained by conversation with the surgeon.

CHANCROID This, in women, has a similar pathologic composition to that of the chancre in men (see chapter on Urinary System), but it is apt to lead to a spreading phagedenic ulcer or gangrene of the vulva that is far more spectacular and extensive than anything seen in men.

LYMPHOGRANULOMA VENEREUM The primary lesion of this venereal disease takes the form of small, round, punched out shallow ulcers on the labia minora or majora near the clitoris. These ulcers are readily overlooked, as they do not as a rule become highly inflamed, and they show no induration or thickened margins. They measure about 6 mm. in diameter. (The lesions in the inguinal glands are described under specific lymphogranulomas, and those of the rectum are considered in the chapter on The Alimentary Tract.)

KRAUROSIS VULVAE A very troublesome atrophic condition of the vulva in elderly subjects, this disease produces a thinned-out,

the acini which are more like hills than papillae may indicate the presence of a carcinoma in the neighborhood, but it is far from constituting proof that there is one there. If one observes such areas it is often wise to advise the removal of the posterior lobe and then to examine this microscopically for the presence of carcinoma.

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18

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TUMORS	UTERINE CURETTINGS FOR DIAGNOSIS OF PREG
VAGINA	NANCY
TUMORS	FALLOPIAN TUBES
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EXAMINATION OF VAGINAL SMEARS	ENDOSALPINGOSIS
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INFLAMMATION (ENDOMETRITIS AND CER	CORPUS LUTEUM
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KRAUROSIS VULVAE A very troublesome atrophic condition of the vulva in elderly subjects, this disease produces a thinned out,

shining, and red appearance in the vulvar epithelium. It affects the labia minora, the frenulum, and the inner surfaces of the labia majora. Beginning as leukoplakia, with thickened firm skin that is white, this later becomes thin, angry red and has the appearance of being shellacked. At first there is microscopic evidence of hyperkeratosis,



Segment of lining of Bartholin's cyst. Epithelium is deep red in section and photographs black here. It is columnar and, in some areas, mucous in type.

which gives way to atrophy. The epithelium which was thickened now shows thinning and absence of rete cones. The epidermal adnexa undergo a similar atrophy. Like any chronic irritative cutaneous lesion, this may become carcinomatous.

CHRONIC ULCERATIVE ELEPHANTIASIS. An uncommon condition, this is also known as "esthiomène." It occurs about the vaginal orifice, more usually in the midline. There is great swelling of the labia minora, with ulcerations on their surface. The fact that the microscopic picture is characterized by the presence of lymphocytes, plasma cells, and giant cells has led to the belief that the malady may be in some way akin to lymphogranuloma venereum.

TUBERCULOSIS AND SYPHILIS. Both of these may be observed on the vulva under rather rare conditions; the former may take the form of lupus vulgaris, the latter of chancre.

Tumors. CONDYLOMA ACUMINATUM. As was explained in the chapter on the alimentary tract, this is a questionable tumor, as it usually follows irritation by excoriating discharges such as that of leukorrhea, and it will recur if not cauterized. It is quite analogous to the same condition in the male. (See "Venereal Wart" under Urinary System.)

NONMALIGNANT TUMORS. Fibroma, lipoma, angioma, tumors of nerves, and pigmented growths appear in that order. The fibromas are apt to be of the soft type, pedunculated and covered by wrinkled skin, and they usually follow some antecedent lesion such as an abscess. They are quite analogous to the all-too-familiar little "anal tabs" that follow or accompany fissure in ano or hemorrhoidectomy. Microscopically they may show a surprisingly large amount of elastic tissue, like that of other soft fibromas. They may attain considerable size and cause a good deal of discomfort. Adenomas originating in Bartholin's glands are uncommon, but recorded in the literature.

MALIGNANT GROWTHS. Carcinoma. Epidermoid carcinoma is naturally to be expected in this situation, and it may arise near the clitoris, the labial folds, or the orifice of the urethra. It has the characteristics of epidermoid carcinoma anywhere. There is usually early involvement of the regional lymph nodes of the groin in contrast to the slowly metastasizing epidermoid carcinoma of the penis. Epidermoid carcinoma is theoretically resistant to x-ray therapy, but it has been found that superficial carcinomas may hold out some promise of cure, as they can be hit directly by the bombardment of x-rays without these having to traverse overlying tissue.

Malignant Melanoma. This may be dismissed with mention; it differs in no way in

this situation from malignant pigmented tumors elsewhere

VAGINA

The congenital anomalies of this structure, as well as its inflammatory lesions, are of little surgical pathologic interest. Chronic inflammation may lead to leukoplakia, which has already been considered in connection with the alimentary tract.

Tumors. NON-MALIGNANT GROWTHS These are of little importance in the vagina, where papillomas of the epithelium and fibromas and aberrant leiomyomas of the wall may be observed.

MALIGNANT GROWTHS *Carcinoma* of the vagina is rather rare and is generally epidermoid in type. It is usually found in the upper posterior wall. Ulceration occurs early, and the tumor is apt to take on a cauliflower like papillary type of growth similar to that seen in cervical tumors of the same category. It carries a very unfavorable prognosis and metastasizes to the ileo pelvic and (should it lie lower in the vagina) inguinal lymph nodes. As the vagina is contiguous to the bladder and rectum, ulceration through the septa between it and those structures may occur and produce very troublesome fistulae.

Seen under the microscope the tumor resembles the plexiform type of epidermoid carcinoma. It possesses a rete of anastomotic cord like or tubular extensions from the basal layer that infiltrates the underlying tissue. Pearl formation and keratosis are not prominent features, and this indicates that the tumor is less well differentiated than many other epidermoid cancers. As there are glandular structures in the upper segment of the vagina that resemble those of the cervix, adenocarcinomatous features may be added to those just enumerated and may account for the tubular extensions just described. There is some question as to whether the adenocarcinomas arise in pre-existing glands or in remnants of the müllerian duct.

Choriocarcinoma This tumor, to be described in connection with the uterus, may spread or metastasize into the vagina.

Sarcoma Sarcoma is infrequently encountered. There is an interesting sarcoma of striated muscular origin that may show additional teratoid elements, such as atypical glands, and is found in the form of grape like clusters of nodules in the vaginal fornix, hence it has been called "sarcoma botryoides." It will be described with rhabdomyosarcoma of the uterus, which it closely resembles.

Cysts There may be a variety of forms met with in the vagina. They originate in rests of müllerian duct or in inclusions of epithelium in the vaginal wall.

EXAMINATION OF VAGINAL SMEARS

Smears of vaginal mucus are now extensively used to determine phases of the menstrual cycle and the presence of carcinomatous cells. The work of Shorr and others on the former and of Papanicolaou and Traut on the latter topic requires mention and description here.

Examination of Cells The taking of vaginal smears is very simple. The instrument used is a glass pipette 0.5 cm. in diameter, 15 cm. in length, slightly curved at its tip, and provided with a stout rubber bulb. Some microscopic slides and a bottle of alcohol and ether (95 per cent alcohol, ethyl ether, aa 50 cc.) large enough to accommodate several slides complete the equipment.

The patient is placed in the lithotomy position, and after the labia have been separated the pipette (with bulb compressed) is introduced into the vagina until the tip is in the posterior fornix. Pressure on the bulb is then released, and the secretion thus is aspirated into the tube. Some of this secretion is then expelled onto one or more of the slides, thicker drops (such as are obtained during menstruation, or in connection with leukorrhea) being smeared out over the surface by means of the convexity of the pipette. Shorr has devised a method

for preventing unevenness in the smears; a drop of equal parts of glycerol and alcohol is first placed upon the slide and the secretion is deposited in this and then smeared out into an even layer. This prevents drying, and the smear may be made in an unhurried fashion. If the aspiration shows enough gross blood to indicate that this will obscure the cellular picture, 2 per cent acetic acid in glycerol may be substituted for glycerol and alcohol. This will lake the erythrocytes and cause their disappearance. When the smears are complete, they are dropped into the alcohol-ether mixture for five minutes' fixation. It does not do to leave them in this for too long (certainly not over a week or two), as the cells will be washed off the glass. Smears are stained by Shorr's method, as given in Chapter 1, or by Papanicolaou's, which will be found in his article in *Science*.

Description of Vaginal Mucosa. The vaginal mucosa is similar to the epidermis of the integument, to the lining of the oral cavity, or to that of the esophagus, being of the epidermoid variety. Unlike these, however, it is not constantly shedding cells from its surface and renewing them by the substitution of others that come up from the basal layer after passing through several phases; instead of this, shedding occurs periodically and corresponds with the menstrual cycle.

The histologic changes in the vaginal mucosa which accompany these cyclic sheddings were first noticed by Morau in 1889. He regarded them as an empiric fact that was observed at the time of ovulation. In 1927 Dierks and Puccioni independently reported changes in the vaginal epithelium which could be correlated with the menstrual cycle. A great deal of argument ensued, Stieve and other authors taking the view that this was an unwarranted assumption. Stockard and Papanicolaou had already correlated similar changes in the vaginas of guinea pigs with their estrous cycles, and it was Papanicolaou who applied these findings to the human patient. In 1935 Davis and Hartman studied these phenom-

ena in the vagina of the Rhesus monkey, the work being later gone over by de Allende, Shorr, and Hartman with a view to correlating the changes noted in monkeys with those observed on human patients in the clinic. The results justify the assumption that both species have almost the same type of cyclic change.

Papanicolaou's method for obtaining and interpreting vaginal smears made it clear that the changes in the picture of the vaginal mucosa could be sampled and evaluated in a much more satisfactory manner than had obtained in connection with biopsies. These had been very confusing, because local biopsies might exhibit very contradictory phenomena; with vaginal smears cells are obtained that have been cast off from large areas of the mucosa and represent an overall picture of what has been going on. Small biopsies taken at random would give variable results referable to small foci of the mucosa only. By charting the readings of smears as curves an even more satisfactory method for evaluating the changes is obtained.

Traut, Bloch, and Kuder have studied these changes by taking selected biopsies and making smears simultaneously, and they have come to the conclusion that there are, indeed, periods of proliferative activity in the basal layer which coincide with the premenstrual phase of the menstrual cycle. They divide the mucosa into a "superficialis" (or "functionalis")—a zone composed of an outer, loose subzone and a deeper, dense stratum; a "light" or intermediate zone; and a "dark" basal layer or "basalis." They find that the basalis begins to proliferate a week before menstrual flow sets in, the superficial layer becoming loosened and reticulated (Shorr says it looks like chicken wire) and shedding off the deeper zone. It seems to be agreed that this shedding involves only a part of the intermediate zone and does not extend down to the basalis, as Dierks has claimed. In some patients the proliferation of the basalis precedes menstruation, while in others it con-

tinues into the menstrual period as well. The rete cones of the basalis grow downward into the submucosal stroma, and the layer becomes generally hyperplastic. The capillaries of the papillae become hyperemic, but this hyperemia is independent of the menstrual flow and is attributable rather to the hyperplasia of the basalis. During pregnancy the mucosa assumes a constant shedding and replacement that corresponds with that of any epidermoid mucosa and takes place more slowly than the cyclic shedding, so that there is gross thickening of the vaginal wall as a result. This is termed "subproliferative replacement."

Shorr, working with de Allende and Hartman, and with Papanicolaou, has made exhaustive studies of the phenomena that may be observed in vaginal smears from a variety of normal and abnormal patients. By employing a stain that will clearly differentiate cornified from noncornified cells he has been able to throw a great deal of light upon the normal and abnormal phases of the cyclic changes in the vaginal mucosa and to utilize his results. These have been applied in connection with the diagnosis of abnormalities and with the evaluation of the efficiency of hormonal therapy in the cases of amenorrhea and dysfunction of the ovaries. In all cases assays of hormonal content of the urine, tests of the basal metabolism, and other clinical tests were employed as counterchecks.

In studying castrates it was found that they possess a very atrophic vaginal mucosa consisting of little more than the basalis. By the administering of estrone this layer may be made to proliferate and gradually to form an intermediate and superficial or functional zone. By the addition of appropriate doses of progesterone to the estrone the superficialis can be induced to become loosened and to shed. Vaginal smears from these patients begin by showing only basal or "deep" cells, under estrone therapy the smears reveal larger but still uncornified cells from the intermediate zone. With continued exhibition of estrone, cornified

wafer-like cells begin to appear. When this is withdrawn there is shedding and the mucosa reverts to its primitive atrophic type. Progesterone produces marked proliferation and shedding, with increased thickening of the membrane, but no cornification. Thus the mechanism of the cycle is well demonstrated.

Vaginal Smears in Diagnosis of Cancer. These smears are also especially useful for diagnosing carcinoma of the cervix and uterus. Papanicolaou and Traut, who discovered this fact, discuss their findings at length in an article listed at the end of this chapter. They place most weight upon the presence in the smears of abnormal, hyperchromatic cells that are unlike any seen under normal conditions. Those from cervical tumors present the most variations in a given smear, as the tumors possess a more heterogeneous composition than do those of the fundus. Cells from the latter are more generally uniform and less widely divergent in size and shape than are those from the cervical growths. By this method it is possible to diagnose carcinoma even when curettage may fail to produce positive evidence. When smears are to be taken from a patient, however, she should be warned not to take any douches before the examination is to be made, otherwise she will wash out the cells and none will accumulate for another 36 hours or so.

In doubtful cases a new procedure, endometrial or endocervical smears, may be employed. These obtain the cells at their source and one has a better opportunity for examining them in their pristine state than is the case when they have been lying about in the vaginal secretions for a while. The material is obtained by means of a minor operation in which a curved metal cannula with one terminal and several lateral openings is introduced into the cervical canal or the endometrial cavity. This involves more risk, of course, than the vaginal smear, which involves none, but it creates less trauma than would the usual curettage. With a little practice any pathologist who

for preventing unevenness in the smears; a drop of equal parts of glycerol and alcohol is first placed upon the slide and the secretion is deposited in this and then smeared out into an even layer. This prevents drying, and the smear may be made in an unhurried fashion. If the aspiration shows enough gross blood to indicate that this will obscure the cellular picture, 2 per cent acetic acid in glycerol may be substituted for glycerol and alcohol. This will take the erythrocytes and cause their disappearance. When the smears are complete, they are dropped into the alcohol-ether mixture for five minutes' fixation. It does not do to leave them in this for too long (certainly not over a week or two), as the cells will be washed off the glass. Smears are stained by Shorr's method, as given in Chapter 1, or by Papanicolaou's, which will be found in his article in *Science*.

Description of Vaginal Mucosa. The vaginal mucosa is similar to the epidermis of the integument, to the lining of the oral cavity, or to that of the esophagus, being of the epidermoid variety. Unlike these, however, it is not constantly shedding cells from its surface and renewing them by the substitution of others that come up from the basal layer after passing through several phases; instead of this, shedding occurs periodically and corresponds with the menstrual cycle.

The histologic changes in the vaginal mucosa which accompany these cyclic sheddings were first noticed by Morau in 1889. He regarded them as an empiric fact that was observed at the time of ovulation. In 1927 Dierks and Puccioni independently reported changes in the vaginal epithelium which could be correlated with the menstrual cycle. A great deal of argument ensued, Stieve and other authors taking the view that this was an unwarranted assumption. Stockard and Papanicolaou had already correlated similar changes in the vaginas of guinea pigs with their estrous cycles, and it was Papanicolaou who applied these findings to the human patient. In 1935 Davis and Hartman studied these phenom-

ena in the vagina of the Rhesus monkey, work being later gone over by de Allen Shorr, and Hartman with a view to correlating the changes noted in monkeys with those observed on human patients in clinic. The results justify the assumption that both species have almost the same type of cyclic change.

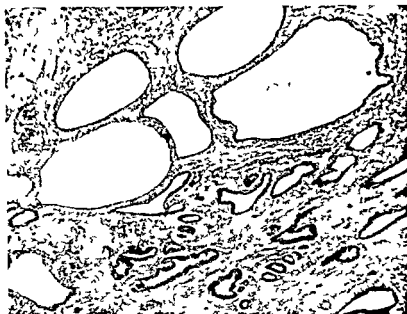
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Syphilis In the female the chancre of syphilis (which has been described in the consideration of the penile portion of the urinary system) usually develops on the cervix. Secondary and tertiary lesions are not commonly noted.

Actinomycosis With the intestinal tract in the neighborhood, the uterus may be come involved in actinomycotic inflamma-

Cervical Polyps As a result of chronic cervicitis (it seems impractical to divide this into endo and ectocervicitis) small adenomatoid growths composed of hyperplastic nabothian glands may be produced. These hang from the cervical tissue, and they may cluster about the external os and produce irritation and inflammation, thus setting up a vicious circle. Sometimes small



Field from endometrium showing cystic degeneration. Uterine lining resembled Swiss cheese on gross examination.

tion, in view of the tendency for these lesions to form fistulae or burrowing tunnels. Actinomycotic appendicitis not infrequently results in such fistulae that not only burrow outward through the appendectomy wound but also tunnel downward into the pelvis communicating with the vagina and rectum. Such extensive invasion may involve the uterus.

Chronic Cervicitis The cervix uteri is frequently chronically inflamed or irritated as a result of postpartum lacerations. When these heal they leave scars that obstruct the nabothian ducts and produce nabothian cysts that are filled with limpid mucus and are thickly studded over the swollen external portion of the cervix. This may be converted into a bi- or multilobate structure by deep lacerations.

true adenomas may form in this situation. The results of either form of "cervical polyp" are about the same. The more usual form is the pseudo adenoma, which seldom exceeds a centimeter in diameter, is ovoid, globular, or spherical, and is usually firm and tough. On section the distended nabothian glands and ducts in these polyps exude a limpid and very slimy and tenacious mucus. They seldom lead to serious trouble, although it must be admitted that they might constitute a focus for the development of an epidermoid carcinoma or adenocarcinoma.

Tumors **NONMALIGNANT TUMORS** *Leiomyoma* By far the commonest lesion of the nonmalignant category is the leiomyoma or "fibroid." It should not be called a "fibro" leiomyoma even though it does

is accustomed to evaluating aspiration biopsies may readily diagnose the presence of malignant growths. He must first acquire familiarity with the normal cells that might be obtained in smears of this sort, in order to rule them out as inconsequential when making his diagnosis.

UTERUS AND CERVIX

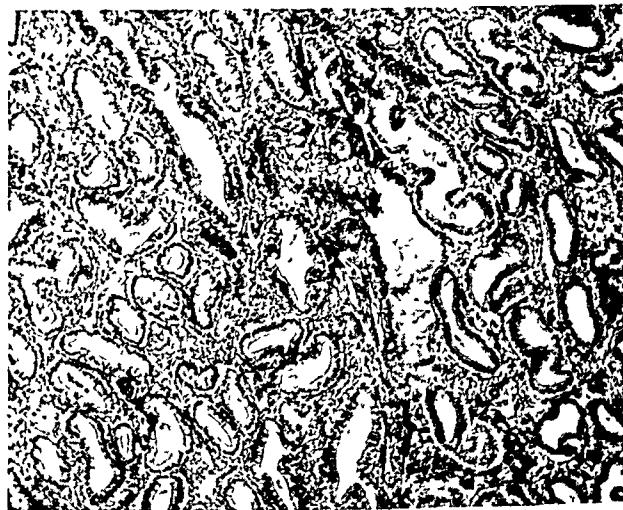
Congenital anomalies of the uterus run the gamut from total absence to the bicornate form resembling that of lower mammals. They are not germane to this discussion.

Inflammation. ACUTE ENDOMETRITIS. This is an acute infection attributable to a number of pyogenic bacteria. It may be very severe and gangrenous, particularly when it follows abortions or the incomplete evacuation of the uterus after labor. It presents the usual characteristics of phlegmonous inflammation and need not detain us further.

CHRONIC ENDOMETRITIS. One occasionally encounters a chronic inflammation of the endometrium, characterized microscopically by the presence of many lymphocytes and plasma cells. It is much more usual to observe changes in the uterine lining caused by faulty hormonal control, these used to be considered "chronic endometritis." The endometrium becomes swollen, fleshy, hyperemic, and edematous. Its surface, when wiped clear of blood, is found to be soft and yellowish and very friable when rubbed with the finger.

It is often difficult to know just what diagnosis to offer for some of the curettings submitted, as they are merely exaggerated forms of familiar cyclic phases of endometrial architecture. In the first part of the intermenstrual cycle the glands are simple and straight, and their cells show basally situated nuclei; later, when progesterone takes over control from estrone, the glands become spiralled and tortuous, the nuclei shift in the cytoplasm and are no longer basal, and the supporting stroma becomes hyperplastic. "Endometrial hyperplasia" is

a condition that merely stresses these phases and exaggerates them. There is a condition known as "irregular maturation" in which the endometrium shows a mixture of these two otherwise well-defined phases, and one may observe areas that apparently represent the early or estrogenic phase, while others are more like the later or progesteronic one. Curettings exhibiting such irregularities usually indicate that the ovar-



The very common "endometrial polyp" or adenoma of the endometrium. It is so well differentiated that it resembles almost normal but superabundant endometrium.

ian functions of the patient should be investigated; possibly a tumor or a cyst might be discovered. Marked endometrial hyperplasia which may attain polypoid proportions is usually indicative of the presence of leiomyoma. A focus of such hyperplasia is known as an "endometrial polyp." Such polyps may become 4 or 5 cm in length and a centimeter or two in diameter and protrude through the cervix. They are very friable and are prone to bleed extensively, even dangerously.

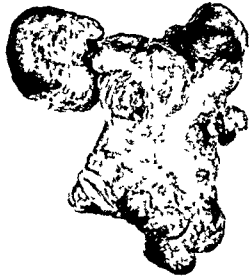
INFECTIOUS GRANULOMA. Tuberculosis. This does not very often originate in the uterus, but is more frequently an extension from the fallopian tubes, where it is not uncommon. It may invade either endometrium or myometrium. It shows the usual microscopic picture of scattered miliary tubercles with only slight caseation.

They may be very dense, homogeneous, and white if very fibrous. When they degenerate, as sometimes happens, they become soft and light brown, with considerable mucinous liquid often contained in irregular clefts and spaces in their tissue.

It is not uncommon to find the uterus invaded by many of these tumors and, in addition, to note that there is a peculiar sheath of curly white tissue resembling compressed wool or Persian lamb enveloping the endometrial cavity like a cap that extends from the fundus almost to the cervix. This appearance is almost pathognomonic of the adenomatous form of leiomyoma called "adenomyoma" by Cullen. If a leiomyoma appears to be in good condition and yet presents a stringy appearance like that of wet bread, and if it contains mucus, this is also usually a sign of the presence of endometriosis in the tumor.

Microscopically, under ordinary conditions the tumor shows a predominance of smooth muscular fibers running in interlacing bundles and sometimes showing palisaded lines of nuclei like rows of soldiers at

right angles to the axis of the muscular fibers. There is always an admixture of fibrous connective tissue which may in time overshadow and replace the muscular ele-



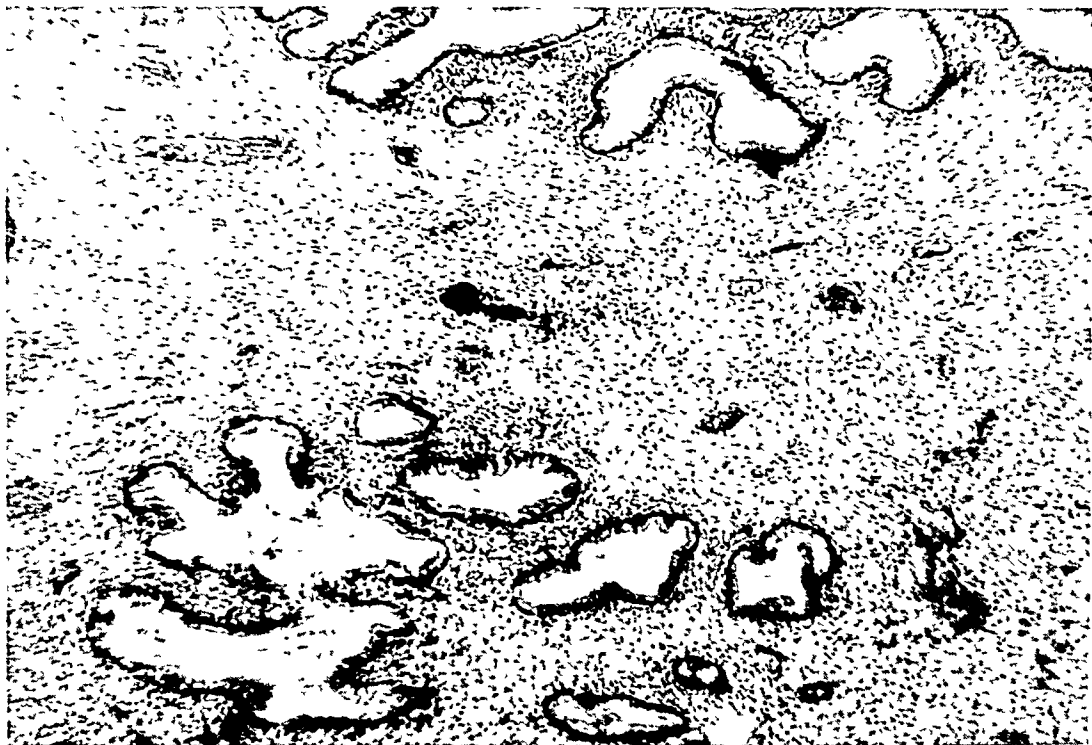
Enormous "fibroid uterus" (over 5 kg in weight). At right middle is right ovary, and at left, abutting on large pedunculated "fibroid," is the left organ. Bulk of specimen comprises enlarged uterus which is studded with fibroleiomyomas.



Section from adenomatous area in leiomyoma of uterus known as "adenomyoma of Cullen." Darker tissue to left is endometrium.

often consist chiefly of fibrous tissue, for the fibrous reaction is much like any desmoplastic response to the presence of tumor. This reaction may become very marked in the case of these tumors and go on to the formation of calcified or even osseous areas, but the underlying tumor growth resides in the muscular ele-

in having a leiomyomatous core. A uterus studded with these tumors is best likened to a hill of potatoes, and a pathologic description of such a specimen often taxes one's ingenuity, so grotesque may be the distortions of the organ and the grouping of the tumors. Leiomyomas may also be found in the broad ligaments of the uterus



A section from typical "cervical polyp." Section is not spectacular and shows nothing beyond hyperplasia of the nabothian glands and increase in fibrous tissue.

ments, for all that. These tumors arise anywhere in the uterus, occurring over a wide age range (fourth to seventh decades). They may be single or multiple, and may vary from a few millimeters to many centimeters in diameter. Usually they cause concomitant hyperplasia of the endometrium.

The tumor is particularly common among Negroes and middle-aged spinsters. It may be situated beneath the serosa (subserous), beneath the endometrium (submucous), or within the myometrium (intramural). Those that lie beneath the serosa or endometrium may become pedunculated; large tumors often spring from a relatively small pedicle. When this is the case in the submucous variety, the tumor may be mistaken for an endometrial polyp, but it differs from this

or retroperitoneally in its vicinity; they may also occur along the course of the round ligaments.

As a rule the tumors make their presence known by symptoms of pelvic discomfort, constipation, and, more importantly, metrorrhagia. Backache is a common symptom. Formerly, leiomyomas were allowed to grow to enormous size before the patient sought relief, but nowadays they are usually removed surgically before they become very large. It is rare to see one that weighs over 4 Kg.

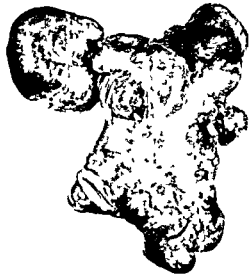
Leiomyomas vary in appearance from firm structures composed of coarse, silvery, interlacing fibers to very hard examples having the appearance (on section surface) of being composed of compressed wool.

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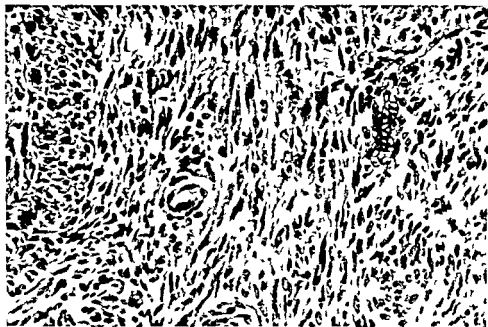
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Rhabdomyosarcoma. Very occasionally and usually in elderly women (I have seen two in the course of 25 years) one may observe large polypoid tumors that spring from the wall of the endometrial cavity and grow rapidly into masses of soft, whitish

The microscopic picture of rhabdomyosarcoma is similar to that seen in these tumors elsewhere in the body, paradoxically it usually seems to be easier to find good examples of well striated myoblasts in these ectopic "maverick" tumors than it is in those of more orthodox parentage that arise in the substance of skeletal muscle. Besides actively growing fusiform myoblasts one



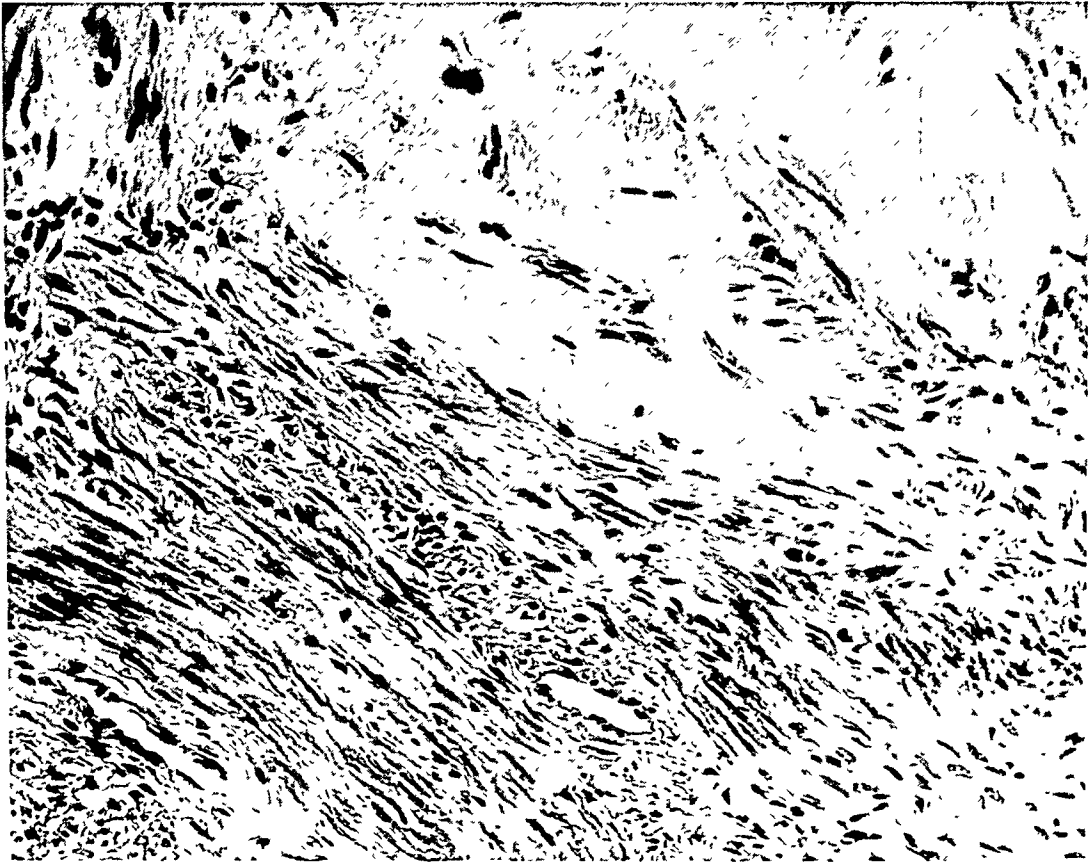
Section from leiomyosarcoma of uterus—a not uncommon tumor. It is rarely malignant in spite of its appearance. Note arrangement of nuclei in rows or palisades. Cells are typical moderately mature leiomyoblasts.

tumor tissue that tends to undergo necrosis and may lead to the discharge per vaginam of large amounts of foul slough. It is usually described as a teratoid growth, but it is remarkably pure striated muscle for such a designation, although muscle gone decidedly wrong. The examination of many normal uteri by those interested in this subject has revealed the presence, particularly in the fundus, of small embryonal rests of adult striated muscle which might be the starting point of such tumors. When, however, they grow in the vault of the vagina in young girls as already indicated, they are apt to be more teratoid and to show a mixture of fibrous and possibly glandular tissue along with the muscle.

also finds large numbers of gigantic, gourd shaped forms with several nuclei and branching stippled fibrils running through a rather unsubstantial cytoplasm. It is important to note that the nuclei of all these rhabdomyosarcomas are very bizarre, large, and hyperchromatic, with very prominent nucleoli that stain vermillion in the Masson sections. Once seen they should not be forgotten, and they constitute a valuable indication of the muscular nature of any malignant tumor that may show them. Only the nuclei of the choriocarcinoma and the pleomorphic type of bronchogenic carcinoma can vie with them for striking and strange appearance. (See illustration in Chapter 7.)

ments. In addition to the elements just mentioned, the adenomatous form contains endometrial glands embedded in the muscular tissue, each group being surrounded by endometrial stroma. Thus we may be dealing with an endometriosis in a muscular tumor, or this may represent some sort of developmental defect that combines gland-

ence. It does occasionally metastasize, however (as he ultimately found out), and when this happens the spread may be very widely disseminated. It is always well, when rendering this diagnosis to a surgeon, to point out that metastasis in the case of leiomyosarcoma is unlikely, and that as he has removed the entire uterus there is nothing more to



Field from leiomyofibroma of uterus. Fibrous tissue is dense and hyaline and shows as whitish area in upper right.

ular and muscular tissue in the same tumor. The propinquity of most of these tumors to the endometrial cavity rather points to the former assumption. The leiomyomas of the broad ligaments do not differ in any way from those of the uterus.

MALIGNANT TUMORS. *Leiomyosarcoma.* This growth has the general gross appearance of a rather soft leiomyoma that has degenerated, but its color is apt to be a characteristic salmon pink rather than light brown or white. It is apt to be more "academically" malignant than really so, and metastasis from the tumor is so rare that F. B. Mallory at one time denied its exist-

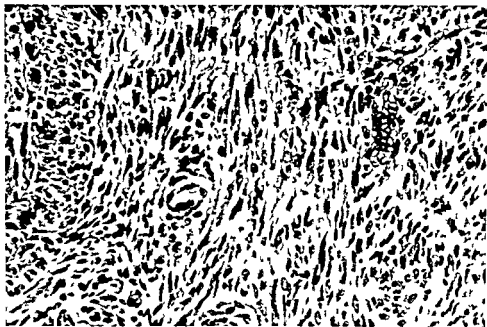
be done beyond keeping the patient under observation.

The microscopic picture of leiomyosarcoma is that of a tumor composed of bundles of long fusiform cells (which may show numerous mitoses) interlaced like those of leiomyoma. There is not much fibrous stroma. Occasional variations from this type-picture are seen: there may be much metaplasia with the production of bizarre gourd-like cells (mentioned in Chapter 17 in connection with nodular hyperplasia of the prostate) or of giant forms; on other occasions the variation is toward a primitive, small myoblast that may be oat-shaped

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Carcinoma. The usual carcinoma of the uterus is that which develops in the fundus of the endometrial cavity as a fungating white growth that is soft and friable, breaking down readily and giving the internal surface of the organ a shaggy and necrotic appearance. It may be associated with leiomyoma, which masks its presence, and it may develop as a result of atypical endometrial hyperplasia. It occurs in later life



Typical area from fundic carcinoma of uterus. It still bears a slight resemblance to endometrial epithelium in spite of its papillary overgrowth.

and does not tend to metastasize early, if at all. Karsner quotes Meigs as having found but four metastatic tumors out of the 44 he examined, so that a round-number percentage of probability of metastasis would be 10 per cent. The tumor may invade the myometrium and penetrate it, sometimes resulting in so friable an organ that it is difficult to remove it without breaking into its substance or tearing the uterus away from the cervical stump. Adenocarcinoma may not be fundic in situation; rarely it arises about the internal cervical os, invading and softening the cervical collar.

Microscopically the tumor is seen to vary from a fairly well differentiated imitation of endometrium to solid masses of cells that fill alveolar spaces and used to be known as "carcinoma simplex" in the German literature. Sometimes, of course, there may be a good deal of pleomorphism in the histo-

logic appearance of the more malignant varieties of the growth. Epidermoid metaplasia may take place, but it is not commonly met with. From women who have been under a long course of estrogen treatment one sometimes obtains curettings in which there is extreme metaplasia of the endometrium so that the presence of carcinoma might well be suspected. In such cases, if the patient is young and there is a history of such treatment, the diagnosis is "endometrial metaplasia from overstimulation." Cancer is not diagnosed. If an elderly woman without any history of hormonal therapy shows this same picture the diagnosis is cancer. Thus we might suppose that the relatively nonmalignant fundic carcinoma may be the outcome of perverted or too intense therapeutic hormonal stimulation.



Undifferentiated carcinoma ("carcinoma simplex") of cervix.

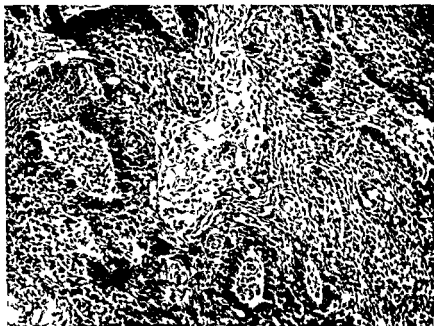
Epidermoid Carcinoma. This is more commonly met with in the cervix and may be found on its vaginal surface or within the canal. It is said to be one of the most common of all carcinomas and, strangely enough, it is one of the few that will respond very favorably to irradiation by x-ray or radon seeds, which may cause the complete disappearance of the neoplasm. Here, trauma is likely to be the etiologic agent. The tumor metastasizes early along the parametrial lymphatics but does not often

reach the inguinal plexuses, it invades the surrounding tissue, extending upward toward the uterus and into the vaginal wall. It forms a fungating, cauliflower-like mass, or it may show a plaque like, ulcerating growth. The latter type is commoner.

Microscopically the growth is like any epidermoid carcinoma and may show a preponderance of the basal elements ("Grade

too mechanical a process and is apt to be misleading.

Choriocarcinoma This very malignant tumor develops in placental tissue and usually in consequence of the delivery of a placental hydatidiform mole, to which it is closely related morphologically, it may, however, follow the retention of secundines after normal pregnancy. Although these are



Full blown epidermoid carcinoma of cervix that occupies a small area in biopsy of that structure

4") or a fair degree of squamous and keratinized differentiation ("Grade 1") There is an early form that develops in the epidermal layers of the cervix and forms small multicentric nests of more or less concentrically arranged cells. This is known as "carcinoma in situ." The variation in the size and shape of the cells of the middle layers of the epidermis resembles the phenomena of the cutaneous lesions of "Bowen's disease" apparently the underlying process is very similar in both instances. We have mentioned "grades," after the method of Broders, but it is far better to give a descriptive diagnosis that will bring the surgeon to the laboratory if there is any doubt in his mind, so that the case may be fully discussed. Issuing grades to surgeons is far

the etiologic factors, there may be a gap of years between the delivery and the development of the tumor. Although this delay may seem mysterious there is less mystery connected with this tumor's histogenesis in the female than there is in the case of the male (see under Tumors of Testis in Chapter 17). Beginning as a small focus, the growth spreads in the uterus or the vaginal vault and may invade the myometrium. It is richly supplied with vascular tissue, as might be expected of an offshoot of placental tissue.

Under the microscope the tumor presents two types of cells. One of them is apparently derived from the Langhans cells of the chorionic villi, but it has become so bloated and bizarre that this connection can

Carcinoma. The usual carcinoma of the uterus is that which develops in the fundus of the endometrial cavity as a fungating white growth that is soft and friable, breaking down readily and giving the internal surface of the organ a shaggy and necrotic appearance. It may be associated with leiomyoma, which masks its presence, and it may develop as a result of atypical endometrial hyperplasia. It occurs in later life



Typical area from fundic carcinoma of uterus. It still bears a slight resemblance to endometrial epithelium in spite of its papillary overgrowth.

and does not tend to metastasize early, if at all. Karsner quotes Meigs as having found but four metastatic tumors out of the 44 he examined, so that a round-number percentage of probability of metastasis would be 10 per cent. The tumor may invade the myometrium and penetrate it, sometimes resulting in so friable an organ that it is difficult to remove it without breaking into its substance or tearing the uterus away from the cervical stump. Adenocarcinoma may not be fundic in situation: rarely it arises about the internal cervical os, invading and softening the cervical collar.

Microscopically the tumor is seen to vary from a fairly well differentiated imitation of endometrium to solid masses of cells that fill alveolar spaces and used to be known as "carcinoma simplex" in the German literature. Sometimes, of course, there may be a good deal of pleomorphism in the histo-

logic appearance of the more malignant varieties of the growth. Epidermoid metaplasia may take place, but it is not commonly met with. From women who have been under a long course of estrogen treatment one sometimes obtains curettings in which there is extreme metaplasia of the endometrium so that the presence of carcinoma might well be suspected. In such cases, if the patient is young and there is a history of such treatment, the diagnosis is "endometrial metaplasia from overstimulation." Cancer is not diagnosed. If an elderly woman without any history of hormonal therapy shows this same picture the diagnosis is cancer. Thus we might suppose that the relatively nonmalignant fundic carcinoma may be the outcome of perverted or too intense therapeutic hormonal stimulation.



Undifferentiated carcinoma ("carcinoma simplex") of cervix.

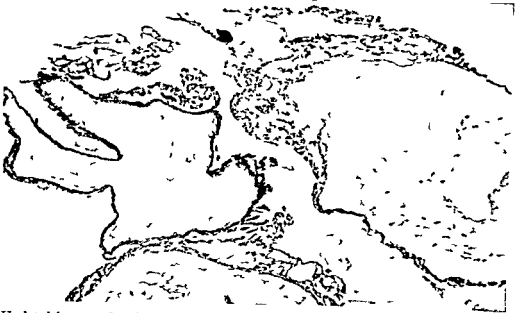
Epidermoid Carcinoma. This is more commonly met with in the cervix and may be found on its vaginal surface or within the canal. It is said to be one of the most common of all carcinomas and, strangely enough, it is one of the few that will respond very favorably to irradiation by x-ray or radon seeds, which may cause the complete disappearance of the neoplasm. Here, trauma is likely to be the etiologic agent. The tumor metastasizes early along the parametrial lymphatics but does not often

as they heal They are attributed to vascular inflammation with or without occlusion and may follow the toxemia of pregnancy

Inflammation Evidence of ordinary acute inflammation may be found in bits of retained placenta that have become infected Tuberculous inflammation is uncommon and readily diagnosed when present Syphi

UTERINE CURETTINGS IN PREGNANCY

A very frequent cause for curetting the uterus is the retention of "secundines," or the secondary products of conception such as bits of the placenta or of the membranes of the fetus Bulky whitish bits of tissue are produced and are sent to the pathologist for diagnosis One must find



Hydatidiform mole of placenta Note edematous villi containing vacuoles and cysts The covering of these, however, retains appearance of that of normal placenta (Courtesy of Dr A A Marchetti)

litic lesions are not readily differentiated from nonspecific ones, and they are very ambiguous in their appearance

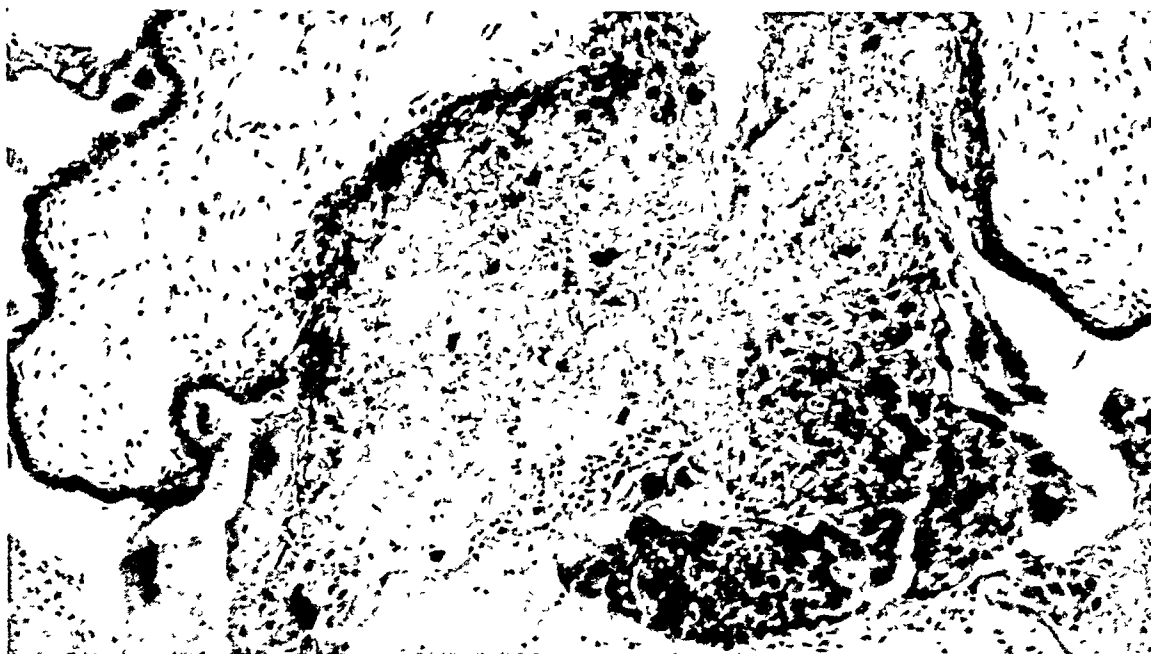
Hydatidiform Mole This (which was mentioned in connection with choriocarcinoma) is usually found among multiparae It is a form of cystic degeneration and hyperplasia of placental villi rather than a true tumor The villi become distended into small bladders that are spherical, translucent, and soft, they spring from slender pedicles that may be elongated Singly they are like hydatids (hence the name of the growth), collectively they remind one of rock sea weed Microscopically there is little to note beyond the fact that the individual villi have become dilated to form cysts and the syncytia are vacuolated

chorionic villi and cells of the syncytial layer in order to make a positive diagnosis of pregnancy As will be seen presently, the discovery of decidual cells either may mean little or may indicate an ectopic pregnancy One could not go into court and maintain a diagnosis of pregnancy in the absence of cells originating in the fetus chorionic villi or the cells thereof

Uterine Curettings in Ectopic Pregnancy The curettings from the uterus of a woman who is ectopically pregnant will show the changes of pregnancy, the conversion of endometrial glands into lacunae or cavernae, and the presence of a well-developed decidua This is not always reliable, however, as curettage taken at some time

scarcely be recognized; its nucleus is very large and possesses thick and prominent karyosomes and a large nucleolus. The other type of cell forms syncytia like those of chorionic villi and tends to show less aberrance from its usual type. Apparently the more active tumor element is the large, metaplastic Langans cell.

The scanty shreds often obtained on curettage seldom if ever reveal any carcinomatous features when examined microscopically, so that a specimen of the bulky, fleshy, and white type should at once arouse suspicion either of retained secundines or of malignant tumor. It is useless to attempt frozen sections on stringy, inadequate ma-



Choriocarcinoma developing in a placental remnant in uterus. The group of large, dark, and atypical cells at lower right is a focus of choriocarcinoma. (Courtesy of Dr. A. A. Marchetti.)

Metastasis is at first local in the vagina, but later becomes widespread in the lungs and other viscera. The urine of patients with this tumor shows increased prolan.

Choriocarcinoma is more malignant than a similar growth (which may also originate in a hydatidiform mole) known as a "chorionadenoma," which is less actively proliferative and is, on the whole, more like such a mole than it is like the choriocarcinoma.

DIAGNOSIS OF UTERINE CARCINOMA IN CURETTINGS. Before this section is concluded it might be well to point out the importance of biopsies in the diagnosis of these tumors. Curettage is the time-honored and usual form of biopsy, and the diagnosis can readily be established on the basis of typical sections, either frozen or paraffin, on curettings that are apt to be fleshy and copious.

terial which is much better entrusted to embedding in paraffin.

The value of vaginal smears has been discussed in connection with the vagina.

PLACENTA

This organ is a staple for pathologic examination in any obstetric service, and usually it proves to be most uninterestingly normal. It may show malformations, variations in form, and deforming lobulations that go under the name of "placenta diparita, triparita," and the like. It may be horseshoe-shaped. Its degenerative phenomena are very common and usually not very significant.

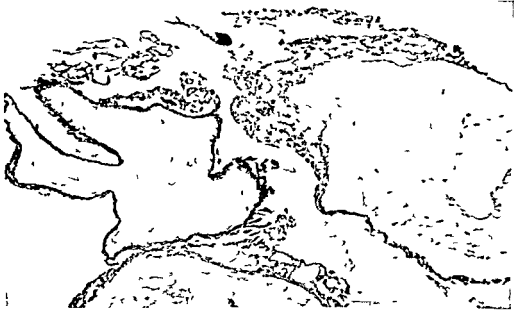
Vascular Changes. "Placental infarcts" are very commonly noted as reddish, hard areas that may undergo necrosis and become yellowish or even fibrotic and white

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after "tubal abortion" will show regenerating, apparently normal endometrium, and it may be difficult to demonstrate the decidual changes. The absence of chorionic tissue is, of course, the crux of the matter, indicating that the placenta is implanted elsewhere than in the uterus—most probably in the tube of one or the other side.

FALLOPIAN TUBES

The oviducts are not the site of many congenital anomalies, and their acute forms of inflammation are usually avoided by any



Acute salpingitis in chronically inflamed oviduct. Mucosal folds are swollen and dotted with leukocytes; mucosa is disrupted. Ultimately tips of folds will be denuded and will coalesce, forming gland-like structures.

surgeon who has made the diagnosis, as an acute salpingitis is better left alone surgically until it subsides. Thus it is the subacute and chronic stages that come to the pathologic laboratory.

Inflammation. CHRONIC SALPINGITIS. Prolonged inflammation by the gonococcus, which is the almost invariable etiologic agent, brings about adhesions between the mucosal folds of the oviducts, agglutination and sealing off of the fimbriated extremity, and marked edema and fibrosis of the wall of the structure. The result of all this is usually an occlusion, possibly proximal as well as distal. Pus accumulates, and a pyosalpinx or "pus-tube" results. The dilated

organ may attain almost twice its normal size and measure as much as 14 cm. in length and 3 cm. in diameter. In certain infections the ovaries may be involved as well, and abscesses may form that include both ovary and tube in a "tubo-ovarian abscess" which can attain a diameter of some 8 to 10 cm. It contains thick yellowish pus and has a ragged and eroded wall. Following this the pus may become sterile with the passage of time and be converted into a watery fluid (hydrosalpinx).

The result of long-standing inflammation of the pelvic peritoneum, which becomes secondarily involved (sometimes including the serosa of the appendix), will be dense adhesions which may "freeze" the pelvic contents. Upon opening the abdomen one will find the pelvic basin roofed over by a mass of apparently inextricably matted loops of bowel, oviducts, ovaries, and uterus. The remote result of such an infection is, of course, sterility; for the sealing off of the distal extremity of both tubes will leave no ingress for the ova.

Microscopic examination of the tube while it is still in an active state of chronic inflammation will reveal the folds of the mucosa to have fused and to have formed many small pseudocysts with cuboidal cells lining them. When the cross section of a tube looks like an adenoma the diagnosis is inevitably chronic salpingitis. The wall of the organ is infiltrated by many leukocytes which emigrate into the lumen; a large proportion of these leukocytes are eosinophils. These tend to remain in the wall, rather than seeking the lumen, as do the neutrophils. Plasma cells and lymphocytes also participate in the exudate which permeates the stroma of the wall. In the plasma cells one may observe Russell bodies.

TUBERCULOSIS. Tuberculous salpingitis is a moderately common form of salpingeal infection. Usually it represents two distributions, both of them, probably, primarily blood-borne: the tubercles are part of a peritoneal tuberculosis and lie on the serosa



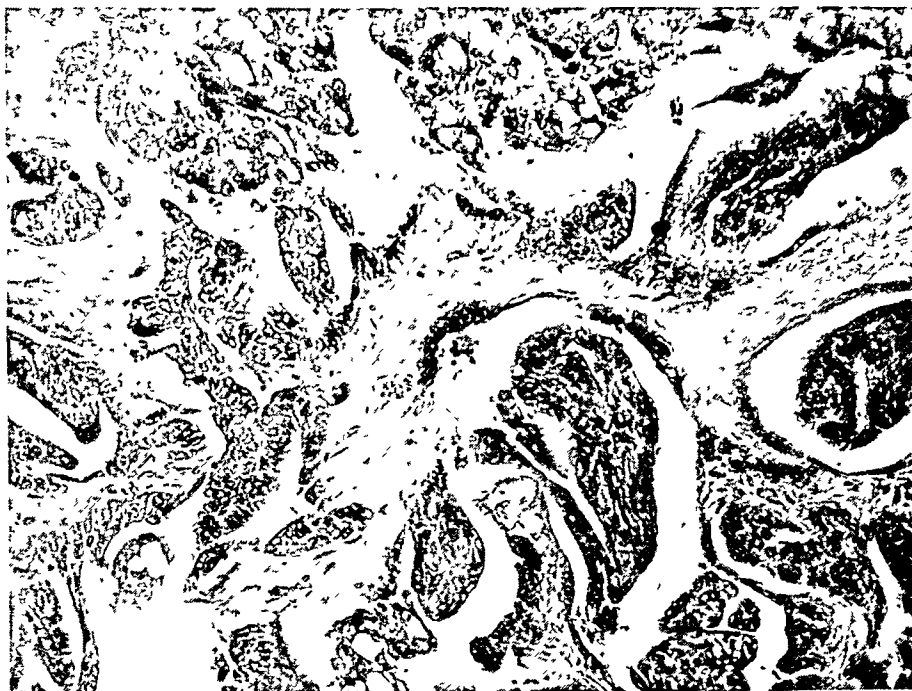
Two typical tubercles in wall of tuberculous fallopian tube In this instance they occupy midportion of wall near muscularis



Field from typical area of tuberculous salpingitis Note small fibrous tubercles and acinoid structures that develop from diverticula of tubal lining epithelium

of the tube or just beneath it; or they may involve the mucosa, apparently avoiding the muscular wall. The process (in its inception miliary) may go on to a state of tuberculous pyosalpinx, the lumen becoming filled with caseous pus, although the usual lesion consists of a large, pale, thickened, and flabby organ that is moist and unhealthy looking. The prognosis is not very serious; usually removal of the tubes results in cure if sup-

it originates in an organ that is already papillary) or an adenocarcinoma. It may form a hard cylindrical mass in the tube or a spherical softer one. The former is less apt to show the papillary form of architecture. These tumors are rare; only one has come into our laboratory in the past twelve years, and it was removed with a fibroid uterus, its presence being unsuspected by the surgeon.



Carcinoma arising in lining of fallopian tube (rare type of carcinoma).

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Endosalpingosis. This is analogous to endometriosis, but differs therefrom in possessing an epithelium that resembles that of the tube, rather than that of the endometrium. The cells tend to show a greater tendency toward ciliation and the stroma is scantier than that of the endometrium. When peritoneal implants lie in proximity to the tubes they may prove to be endosalpingeal.

Tumors. NONMALIGNANT GROWTHS. These are remarkably rare; adenomas, fibromas, and angiomas have been reported.

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The microscopic appearance of tubal carcinomas is (as indicated above) either one of papillary adenocarcinoma or one of a rather simpler adenocarcinomatous structure. In either instance it is composed of cylindrical cells that are enough like normal tubal cells to make the diagnosis relatively simple, as they give the growths a distinctive appearance. These tumors are notorious for penetrating the wall of the oviduct or escaping from the "trumpet" and spreading rapidly over the peritoneal surface. They may also invade the regional iliac lymphatics. Therefore they bear a distinctly ominous prognosis and usually terminate fatally a short time after their discovery—a period seldom to be reckoned in years.

Ectopic Pregnancy This is unfortunately fairly frequent in its incidence and can have very serious consequences from the hemorrhage that it initiates. Although the ovum is impregnated in the oviduct under normal conditions, it is unusual for it to stay there after fertilization, should it do so, however, it forthwith forms a placenta wherever it may have lodged. The usual

been considered under the section devoted to that organ.)

The specimen obtained at operation will present a tube that may be enlarged, with a generous mass in its lumen, or may be of normal size, with the trophoblast and its membranes attached to the fimbriated extremity—possibly to one fimbria. Microscopic examination reveals more blood clot



Transverse section through a midtubal pregnancy in approximately its third week. Embryo lies in pool of blood at center of picture. Its notochord is plainly visible at the upper left of hourglass like section through embryo.

site of implantation is toward the distal end of the oviduct, if this occurs at the isthmus its explosive propensities are enhanced by lack of room and the rupture of important arteries in the neighborhood, which occurs early, if it takes place in a distensible and relatively roomy segment it will be more advanced in its development when the eventual rupture of the tube or trophoblastic membranes takes place. It may slip out into the peritoneal cavity, where pregnancy has been known to continue to term, the placenta attaching itself to the mesentery. The trophoblast may rupture into the tubal lumen (tubal abortion), causing a form of hematosalpinx. Rupture of the wall of the oviduct occurs in about 25 per cent of ectopic pregnancies. (The uterine manifestations of ectopic pregnancy have already

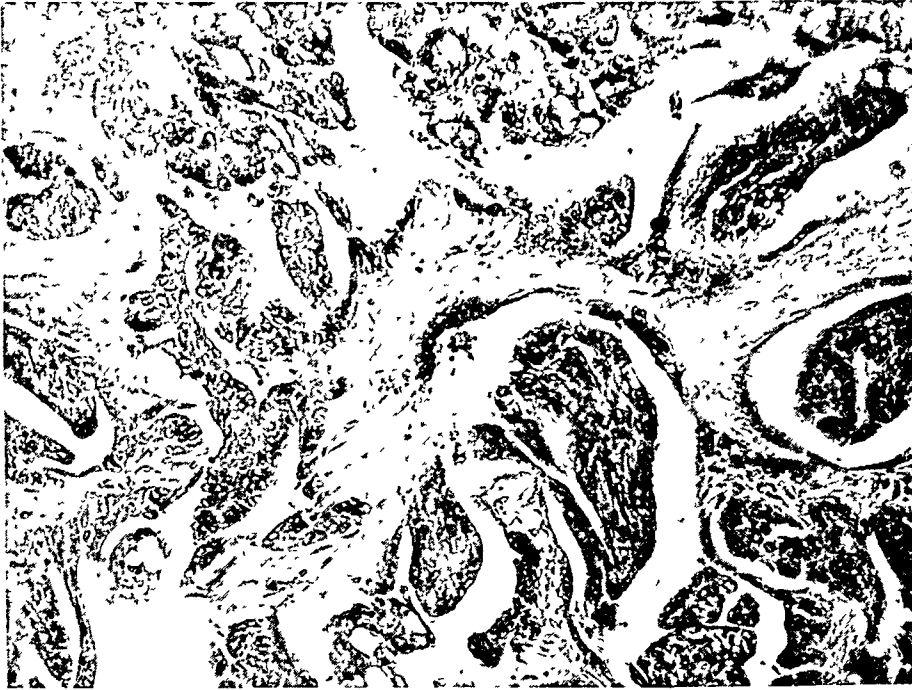
than anything else, as the products of conception undergo necrosis and disappear early in the proceedings. If a placenta has had time to form, the typical chorionic villi will furnish positive evidence, otherwise it may be necessary to make a logical diagnosis, rather than a documented diagnosis based upon the clinical features of the case and the presence of a positive pregnancy test (Aschheim Zondek or Friedman).

OVARIES

Corpus Luteum One of the most frequent "pathologic" specimens removed from ovaries and submitted to the laboratory is a corpus luteum (as often as not one of pregnancy) into which there has been considerable hemorrhage, with the formation of a blood cyst about 15 mm in diameter

of the tube or just beneath it; or they may involve the mucosa, apparently avoiding the muscular wall. The process (in its inception miliary) may go on to a state of tuberculous pyosalpinx, the lumen becoming filled with caseous pus, although the usual lesion consists of a large, pale, thickened, and flabby organ that is moist and unhealthy looking. The prognosis is not very serious; usually removal of the tubes results in cure if sup-

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Group of endometrial glands with stroma (the former much dilated) from an area of endometriosis in ovary. Hemorrhage into cysts produces the "chocolate cyst" of surgical parlance.

the finding of menstruating endometrial tissue in the umbilicus after gynecologic laparotomies (as reported by Weller and observed by myself) favors Sampson's view. Possibly both theories have a sound basis and apply in appropriate instances. Metaplasia of the peritoneal cells seems the least probable idea.

The cysts begin as implantations of small foci of endometrium which bleeds at the regular menstrual periods. These foci may gradually form cysts that may attain considerable size and are filled with a mass of sticky, sepia colored material which (when there is admixture of blood) resembles chocolate enough to give rise to the name "chocolate cysts." Polster has found records of such cysts in the ovaries, tubes, broad ligament, inguinal region, laparotomy

scars, rectovaginal septum, vesicovaginal septum, umbilicus (thirty records), and intestinal peritoneum. The cysts may grow to 9 or 10 cm. in diameter.

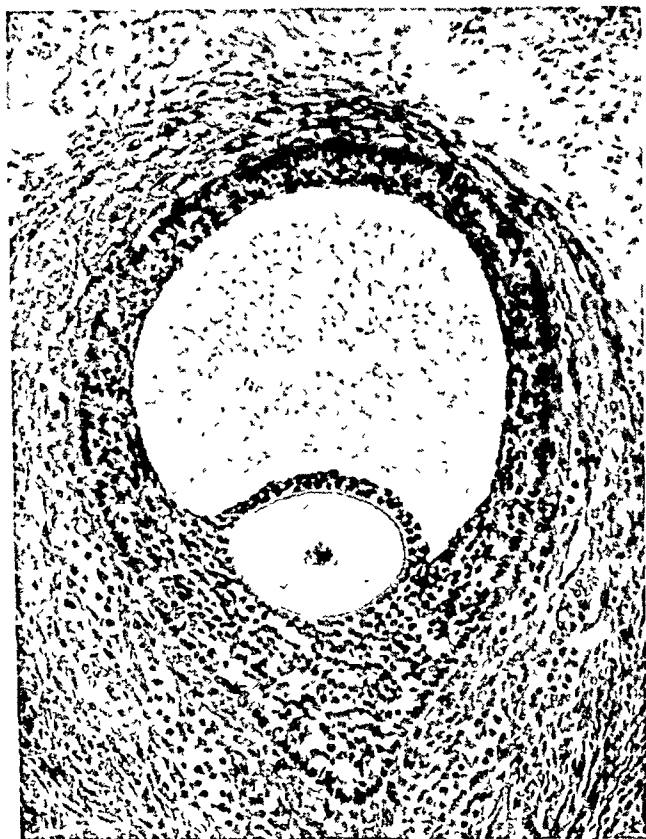
The microscopic picture is that of a cyst lined with cuboidal cells which are more or less flattened out. Here and there one will find recesses that betray the nature of the cyst by presenting unmistakable insets of endometrium containing cylindrical cells some of which are ciliated, some "bald," and all overlying a variable quantity of endometrial stroma of typical appearance. In some instances this anomalous endometrium may apparently originate in the oviduct, as already mentioned.

None of the above described cysts qualify for consideration as tumors, they all result from dyscrasias of the graafian follicles and of the lining membrane of uterus and tubes.

PAROVARIAN CYSTS These are common little structures originating near the fimbriated extremities of the tubes in the broad ligament and representing retention cysts in tubules of the parovarium. Thin walled and inconspicuous, they resemble the hydatid cysts of the epididymis, they may become twisted and strangulated, but usually they are an incidental finding of little importance. Microscopically they are found to be unilocular cysts lined by a single layer of cuboidal epithelium in which cilia are often demonstrable. True tumors of the parovarium are rare, although carcinomas and sarcomas may arise from it. Fibroadenomas and papillary cystomas as well as teratomas, may also be situated here.

Tumors Until Robert Meyer began his work on these tumors, the subject might have been termed chaotic and the classification more so. The ovary, like the testis, is a gonad possessing two functions. The ovary's two functions are the production of cells that reproduce the species and the internal secretion of sexual hormones. The cells that serve the latter purpose fail to form acinar structures like glands of external secretion, they are more like those

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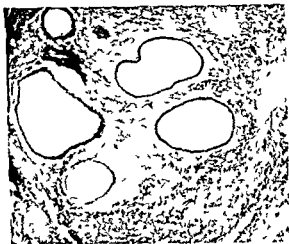
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CYSTS OF CORPUS LUTEUM. The early stage of these has been described above; after the blood has become liquefied it is largely converted into a limpid yellowish fluid that may contain some cholesterol and is not unlike that of so-called "blood cysts" anywhere else—in thyroid adenomas, for example. With time the tendency is for the lutein cells lining the cyst cavity to disappear and for the cyst to become lined with more or less naked connective tissue. The presence of hemosiderin within cells lining the cyst usually affords a diagnostic criterion. These are often mistaken by surgeons for endometrial cysts.

THECA-LUTEIN CYSTS. These appear to have some connection with the presence of hydatidiform mole and choriocarcinoma, as they usually occur when one of these is present. Their differentiation from follicular cysts is not very clear, but apparently resides in the fact that they are lined by theca cells, which take up lutein pigment and form small masses that do not exhibit the convolutions of the ordinary corpus luteum.

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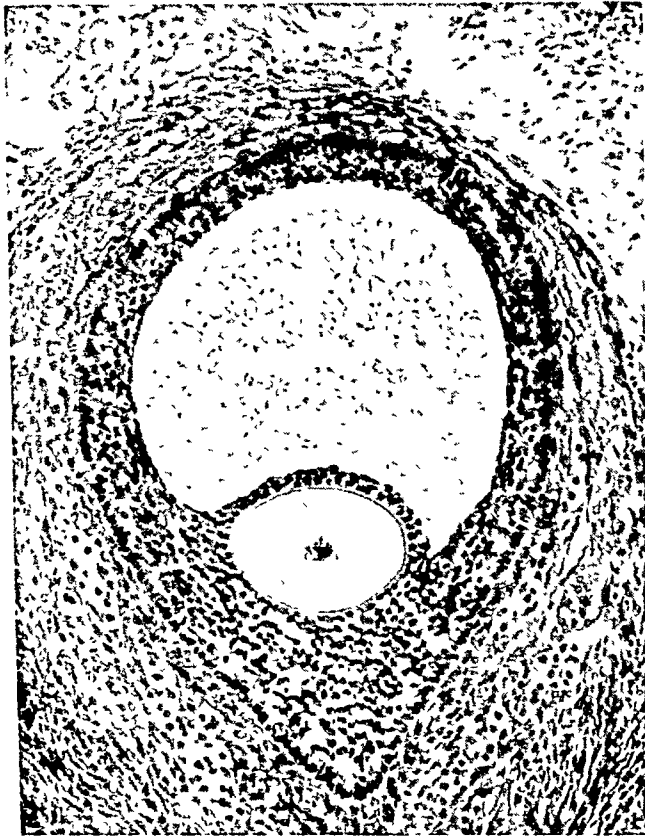
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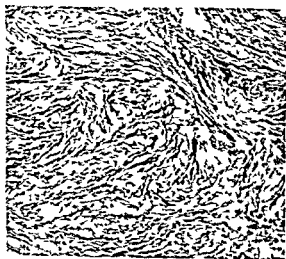
Granulosa celled carcinoma of ovary There is lawless overgrowth of cells which have vague resemblance to those of a graafian follicle Metaplasia disguises much of this similarity
Note numerous mitotic figures

fibroma There is a reason for this, as theca-cells are probably closely related to connective tissue elements, Traut and Marchetti have shown that they produce an abundant reticulum and, as they form the outer layer of the follicle, have connective tissue functions In the tumor, however, they tend to be more or less lipoidized, this gives the growth a yellowish tinge They, too, produce changes in the endometrium, myometrium, and breast resembling those which accompany granulosa cell tumor

Microscopically the tumor is composed of epithelioid or fusiform elements which take up a variable amount of lipoids and tend to be arranged in bands or fascicles The tumor shows abundant reticulum not unlike that of connective tissue tumors, and there may be fields of hyaline degeneration Theca cell tumors are rated as being comparatively rare, their malignant variety even more so

GROUP 2 Arrhenoblastoma Arrhenoblastomas are of disputed origin, grossly the type resembles the granulosa cell tumor, but microscopically it is entirely different

Its presence causes virilizing symptoms changes in the voice to a lower hoarser pitch and quality, male implantation of pubic hair with hirsutism of the face and body, and a generalized male habitus and build, with atrophy of the breasts and of the adipose tissue of the thighs and buttocks



Typical theca-celled tumor of ovary It resembles fibroma, but has distinctively interlacing architecture and paler, washed-out staining reaction

of the paraganglionic secretory cells in their morphology. For this reason, the tumors that arise in the organ may resemble glands in many instances, but these resemblances are not sufficient to warrant the assumption that they form "adenomas" or "carcinomas." They are much more closely related to embryonal rests, inclusion tumors, and other such growths that give such impetus to the original theories of Cohnheim and Ribbert as to the origin of neoplasms.

In a recently published atlas of ovarian tumors Barzilai presents a classification that is logical and appealing, as it indicates the origin of these tumors, whether or not this be definitely proved. The result is orderly and stimulating. She divides the neoplasms into seven categories:

1. Tumors traceable to developmental and cyclic phases of the graafian follicle: granulosa- and theca-cell tumors.
2. Growths traceable to the developmental stages of the male gonad: arrhenoblastoma and "virilizing lipoid-cell tumor," which she properly marks "(?)."
3. Tumors of completely dedifferentiated and very primitive cells seen in the early mesenchymal core of the ovary: dysgerminomas.
4. Neoplasms traceable to the development of totipotent or multipotent cells such as those of a somatic embryonal blastomere: teratomas of the adult or embryonal type.
5. Growths attributable to connective tissue of the extrafollicular stroma of the ovary: fibromas and sarcomas.
6. Tumors derived from cells that may be found in organs adjacent to the ovary in adult life or intimately associated with it during embryonal development (müllerian, wolffian, and enteric tissue): Brenner's tumor (muroid fibro-epithelioma), endosalpingioma (serous cystoma), seroanaplastic carcinoma (serous carcinoma), pseudomucinous adenoma and adenocarcinoma, pseudomyxoma ovarii et peritonei, and mesonephroma (embryonal

carcinoma). (The names commonly used are in parentheses.)

7. Tumors traceable to secondary involvement of the ovary by metastasis from other organs: Krukenberg's tumor, other metastatic growths.

It would be well to utilize this clear classification in the ensuing description, making some modifications where this is considered best. In this way confusion will be minimized, the presentation will be systematic, and the usual untidy appearance of descriptions of these tumors will be avoided.

GROUP 1. Granulosa-cell Tumor. This generally appears near the menopause, although it may develop at any time of life; when it occurs in childhood its presence is associated with precocious development of the secondary sexual characteristics and irregularly periodic bleeding from the vagina. In adult life there is irregular menorrhagia, or metrorrhagia that may be more or less continuous. The tumor is solid, white, and firm, with a diameter of 10 cm. or more. Its presence stimulates endometrial hyperplasia; this accounts for the uterine bleeding.

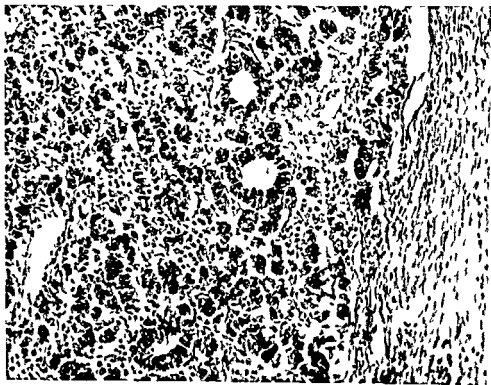
The microscopic appearance varies; at first glance it might be taken for a carcinoma, but close examination shows that the cells are remarkably uniform in size and shape and that they show variable grouping, sometimes about a lumen, sometimes in solid masses, and sometimes in strands that are almost sarcomatous in appearance and in which the cells are definitely fusiform. Barzilai subdivides them into many morphologic subgroups: macrofollicular, trabecular, diffuse sarcomatoid, medullary, "moiré silk," and so on. These are all variations on a basic pattern which, of course, is that of the graafian follicle. Some of them show lipoid infiltration or luteinization. There are mature and nonmalignant types, as well as immature and malignant types that may metastasize.

Theca-cell Tumor. This may be unilateral or (rarely) bilateral; it usually appears after the menopause, looking much like a

similar to those produced by progesterone have indicated possible follicular origin for the tumor, there is considerable confusion as to its histogenesis. In fact, this growth serves only further to obfuscate the entire question of "hypernephroid" tumors.

GROUP 3 *Dysgerminoma* This neoplasm so closely apes the appearance of the dys-

GROUP 4 *Teratoma* Ovarian teratoma is like the adult form of testicular teratoma already described. From this it differs in no way and may be of the "embryonic" form described in that connection. Its most usual manifestation is that commonly known as "dermoid cyst," in which the tumor is chiefly composed of a cyst or group of cysts



Area from arrhenoblastoma of ovary showing fully developed testiculoid tubules (Courtesy of Dr. A. A. Marchetti)

germinoma of the testis that there is no need for elaborating on its minute appearance. It has been known by all the names applied to that tumor. A decidedly rare growth, it affects young people and may be associated with dyscrasias in sexual development which may be very marked, such as absence of the oviducts or uterus or of a contralateral ovary. It is often bilateral. The tumor is very malignant and almost invariably spreads via the lymphatics, rather than the blood.

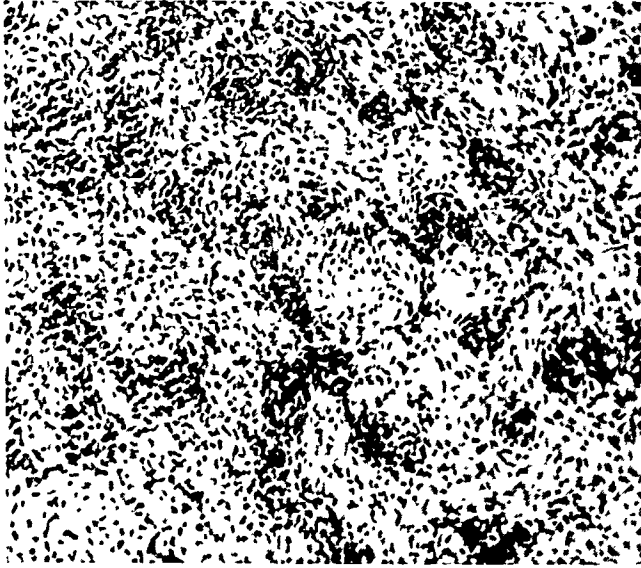
Microscopically it most closely resembles the testicular seminomas and embryonal carcinomas, occasionally showing the lymphoid stroma of the latter.

lined with skin from which abundant hair grows from a scalp like plaque that is raised above the level of the surrounding lining at one point and measures 2 to 4 cm. as a rule. Mixed with this hair is a mass of either caseous or oleaginous material resembling vaseline or olive oil, so that palpation of such a growth gives one the sensation of squeezing a bag of soft putty. The tumor varies in size, is well encapsulated, and replaces the ovary which is usually found flattened out at one side of the wall.

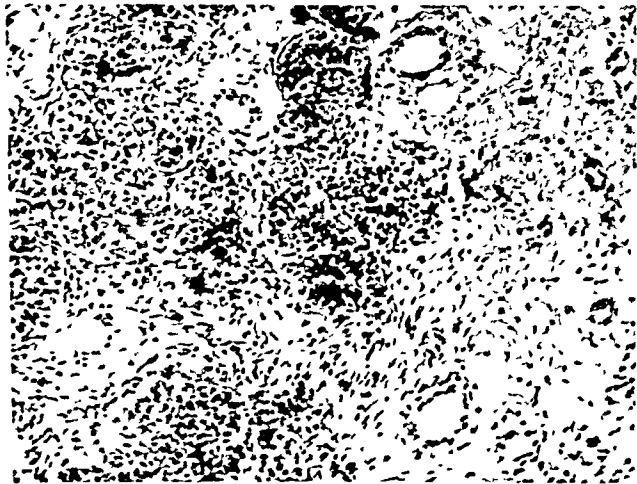
Dermoid cysts are often accidentally discovered at operation. Besides the constituents just enumerated, bone and teeth may be noted on gross inspection, usually form

Amenorrhea is usual. These symptoms usually subside after removal of the tumor.

The arrhenoblastoma is a rare growth, only fifty or so having been reported and



Area of primitive gonadal tissue in arrhenoblastoma of the ovary. It resembles dysgerminoma. (Courtesy of Dr. A. A. Marchetti)



Another field from arrhenoblastoma of ovary showing early differentiation of cells into tubules resembling testicular primordium. (Courtesy of Dr. A. A. Marchetti.)

none having been observed in our laboratory thus far. It occurs between the ages of 15 and 60, is usually unilateral and varies in diameter from a few millimeters to 20 mm. or more. It is smooth, bluish or yellowish in color, and does not tend to adhere to surrounding structures. Its section surface

is mottled reddish and bluish, and its consistence is firm in the small examples, softer in those of larger size.

Three main histologic patterns may be differentiated: an undifferentiated one like a fibrosarcoma and resembling the early primordial tissue of the testis; an intermediate type in which large epithelioid cells begin to form cords or even imperfectly formed tubules in a sarcomatoid matrix, and a definitely tubular variety in which the tubuli contorti of the testis are reproduced to some degree. The cells comprised by these tubules, however, more closely resemble the sustentacular Sertoli cells than they do the spermatogonia; thus they are reminiscent of the microscopic picture of undescended testis.

The histogenesis of the tumor is uncertain; it has been attributed to the persistence of male gonadal cells in the ovary, to a development of the male portions of the ovotestis sometimes noted in hermaphroditism in which a rete testis will be present in the ovary, or to a displaced rete testis. On account of its undifferentiated microscopic appearance, the arrhenoblastoma is usually classed as malignant; as a rule, however, it does not metastasize, although there are a few instances of this on record.

Suprarenal Inclusion Tumor. This growth, also known as "virilizing lipoid-cell tumor," is a very rare one, but it makes up for its rarity by producing dramatic virilizing symptoms like those occasioned by the arrhenoblastoma. Like them, these symptoms promptly subside after removal of the tumor. The growth, which may appear at any period in the life span, is seldom malignant; it is usually unilateral, may be single or multiple, and, although generally of small size, may grow to large proportions.

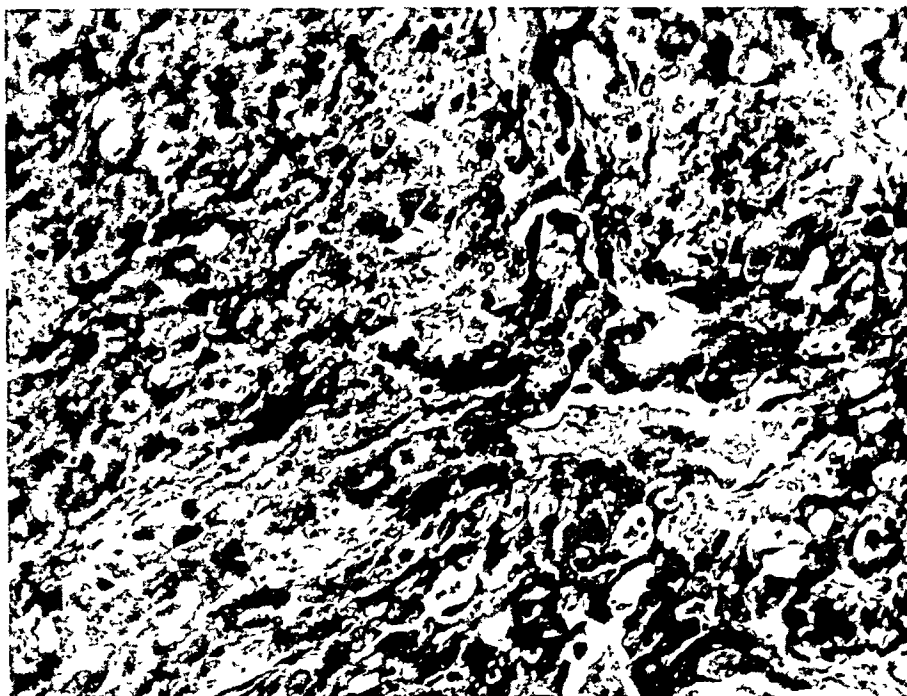
Microscopically it is strikingly like "hypernephroma" in its appearance and staining characteristics, including the presence in its cells of lipids and glycogen. As suprarenal and Leydig-cell rests have both been demonstrated in the ovary and as effects



Field from ovarian teratoma or "dermoid cyst." At center is a bit of solid bone, to left are sebaceous glands, to right of center are mucous glands, and in right lower corner is a cyst of a somewhat intestinal appearance



Another field from same ovarian teratoma, showing well developed cancellous bone with marrow, embedded in fat. Mass of nervous tissue occupies left side of field



Dysgerminoma of ovary that somewhat resembles chorionic type of testicular dysgerminoma shown on pages 347 and 348.



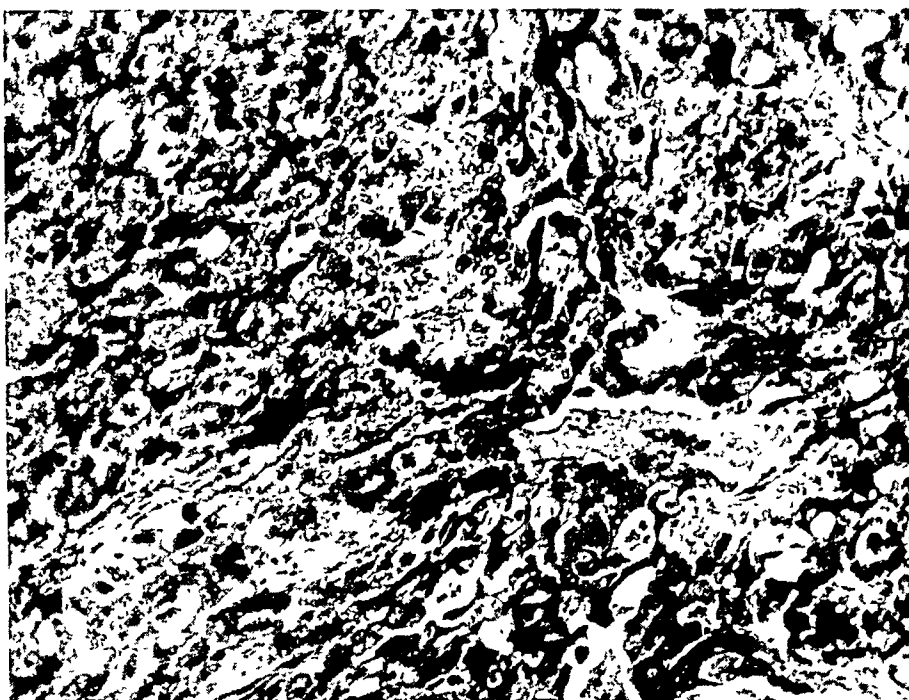
Section from wall of "dermoid cyst" or teratoma of ovary. Grayish tissue at left is of neural origin and resembles cerebral tissue; to right is a group of sebaceous glands which secrete oily contents of cyst. Large cysts at the upper middle are dilated sudoriferous ducts, and black structure at upper left is a hair follicle.



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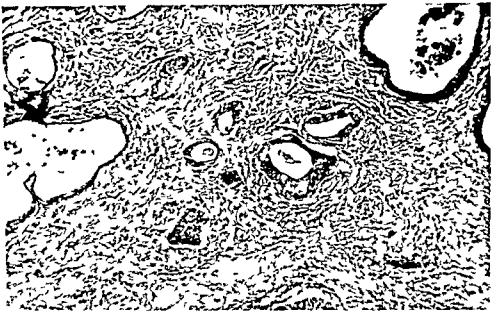
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consisting of clear paramalpighian cells which constitute a palisade about a central core of undifferentiated cells of the same origin, and this may contain a microcyst lined with cuboidal epithelium. These units are not always readily found. Elsewhere the tumor shows cells arranged in cords or masses, or in cysts containing the mucus that gives the growth the appearance of a

pingioma." It is one of the commonest ovarian growths, being encountered a little oftener than the pseudomucinous cystoma, with which it comprises the bulk of ovarian tumors in surgical material. It usually arises during active sexual life and during this period shows an actively growing papillary form, while in later years the walls of the cysts are usually smooth, with small,



Section from "Brenner" tumor of ovary. At center is a group of Walthard bodies (also known as "paramalpighian cell aggregates"). The larger cystic cavities are partially filled with pseudomucin.

pseudomucinous adenoma in some areas. These epithelial complexes are embedded in a dense fibromatous stroma that is very well differentiated as a rule. They are of three general types: paramalpighian, pseudomucinous, and serous, so that the tumor in a way combines the elements of two other ovarian neoplasms in its composition. There are several theories as to the origin of these growths: that they originate from the wolffian body through the rete ovarii, from remnants of the müllerian ducts, or from the superficial epithelium of the ovary and aggregations of Walthard cells. The tumor is almost always nonmalignant.

Scrous Cystoma. This is the usually accepted term for a tumor which Barzilai (for reasons to be given later) calls "endosal-

warty, white excrescences scattered at intervals over the inner surface.

The usual types are uni- or multilocular cysts that are generally unilateral and may attain considerable size. They may be smooth on the inside or lined with papillae, and their contents are almost always a thin, watery liquid that may be brownish in the larger, older, and more traumatized cysts. The growth is often intraligamentous and may be pedunculated. If it ruptures and papillae are cast off into the peritoneal cavity, daughter cysts may grow and cause ascites; they will be found as scattered implants on the peritoneal surface.

The microscopic appearance is decidedly reminiscent of the tubal epithelium or endosalpinx. The smooth portion of the lining is

ing a small stony mound in the wall—the “dermoid plug.” The contained hair usually corresponds in color and texture with that of the patient.

Microscopic examination reveals a variety of pictures: in the simpler “dermoids” one finds skin and its adnexa, nervous tissue resembling neuroglia, and bone, cartilage, or teeth—all of which indicate development from cells destined for the cephalic portion of an embryo. In the more complicated and better-differentiated teratomas one need not be surprised to find almost any form of tissue; indeed sections of some of these might well serve as a review of histology.

It is not unusual to find certain cell groups in a teratoma that may exhibit malignant characteristics and, as a result, cause metastases that are more in the nature of dysgerminomas than of teratomas. Carcinomas of various sorts have been known to develop from the skin or glandular epithelium of teratomas. Barzilai distinguishes an “embryonal type” of teratoma as contrasted with the “adult type.” In the former the tissue shows less organoid differentiation, malignant areas are present that may metastasize (sometimes as choriocarcinomas), and the growths occur in younger patients. Here the term “embryonal” is used in its usual sense, indicating lack of cellular differentiation. The tumor probably originates in gonadal cells, ova, or primitive epithelium from the surface of the ovary that underlies these.

GROUP 5. *Fibroma.* This is a relatively common tumor of the ovary and occurs in elderly women. It differs so little from fibromas in general that a lengthy discussion is not indicated. Suffice it to say that it has more the appearance of dense ovarian stromal tissue than do most fibromas, its cells growing in very compact masses and producing a diffuse growth of collagenous fibers. Hyaline degeneration and calcification are common phenomena.

In connection with such tumors one observes a clinical syndrome to which Meigs has called attention and which goes under

his name; in this ascites develops, followed by hydrothorax. This is unexplained, but apparently it is connected with the presence of the tumor, as surgical removal of the growth is promptly followed by subsidence of these signs. Therefore, unexplained hydrothorax in a woman should always indicate the necessity for a thorough pelvic examination.

Fibrosarcoma. Unlike fibroma, fibrosarcoma is extremely rare as a primary ovarian growth. Barzilai could find only three examples among the 10,000 ovarian tumors she examined. Naturally it is readily mistaken for more specialized ovarian neoplasms like the theca-cell tumor, and the reverse is also true, which may be the reason for confusion.

If the growth is of the definitely fibrous type it is usually unilateral, firm, and grayish white; if, however, it is more undifferentiated it is very friable and extends from the ovary into the neighboring tissue. Microscopically it resembles any fibrosarcoma, with cells that vary from a fair reproduction of fibroblasts to very metaplastic forms that are swollen and distorted.

GROUP 6. *Mucoid Fibro-epithelioma.* This tumor, usually known as “Brenner’s” or, as Plaut has suggested, “fibro-epithelioma mucinosum ovarii,” is a nonmalignant one that generally attacks women shortly before or after the menopause and is to be considered among the rarer ovarian tumors. It is almost invariably unilateral and may present as almost microscopic nodules that are fairly frequently noted in carefully examined ovarian sections; or it may appear as a huge variety that almost fill the abdominal cavity. It differs from most of the ovarian tumors in its association with other varieties of tumor in the same ovary or genital tract. It may be solid and yellowish white; or it may have a “Swiss cheese” appearance, the loculi being filled with clear mucoid material that drips over the section surface; or it may be almost entirely cystic.

There may be a good deal of variety in its microscopic appearance. There is the characteristic “unit form” of architecture

"bizarre" or "wild" In short, the variations are in accord with the degree of malignant change in the epithelium

The histogenesis of this new growth is probably similar to that of the serous cystoma. It is a tumor in which there may be seeding out over the peritoneal surface covering vital organs, and if this has taken

average patient now appeals for treatment when it is 10 to 15 cm in diameter. It is usually well pedunculated and may be intraligamentous or project from the ovary into the abdominal cavity. It may be unilocular or multilocular and lined by either a smooth membrane or one studded with papillae, it may show areas that are solid



Serous carcinoma ("sero-anaplastic carcinoma") of ovary. This is a cellular and solid form of this tumor.

place it makes complete extirpation impossible.

Pseudomucinous Adenoma This is usually a bulky and cystic tumor composed of cysts and glandular complexes that secrete an abundant pseudomucinous material resembling mucus and varying from a limpid fluid of glairy consistence to dense, brownish, or greenish brown and very viscous masses that are not unlike the contents of an obstructed gallbladder. It most often affects women between 30 and 60, occurring during the period of sexual activity. It is almost as common as the serous cystoma and may reach enormous dimensions; it is not uncommon to see such tumors attain diameters of 50 to 60 cm, although the

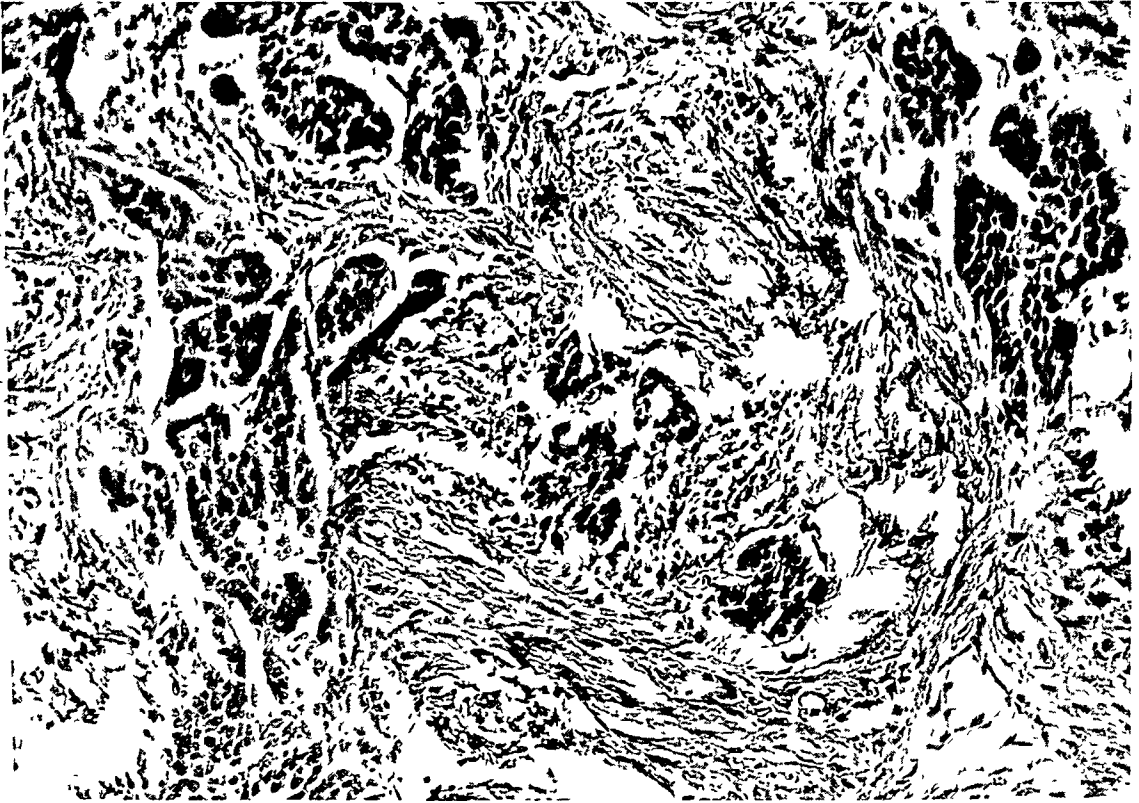
and contain glandular tissue. The chemistry of its contents reveals three types of pseudomucinous substances, Lecene, Moulouguet, and others have shown that it includes enzymes (sucrase or invertin) that are normally found only in the intestinal mucosa.

The microscopic picture reveals the tumor to be composed of glandular structures and papillae made up of clear columnar cells that are identical in their appearance with those of the cervical glands. They may show various secretory phases, in one of which goblets are developed, as they are in the intestinal mucosa. The fact that Danforth could demonstrate structures in this growth resembling the Walthard cell nests of the Brenner tumor, with columnar cells pal-

composed of cuboidal cells that may be considerably flattened, while the papillary areas show cells that may or may not be ciliated. Barzilai illustrates many varieties of these cells in her atlas, stressing their resemblance to the salpingeal lining; she admits that this may be fortuitous. Theories as to the origin of the tumor attribute it to

apt to show very strange and new forms that could not be observed in normal embryos. Therefore "serometaplastic" or "metaplastic serous carcinoma" would be more logical.

Macroscopically the tumor is not very different in its appearance from the non-malignant serous cystoma; often one must await the completion of microscopic sections



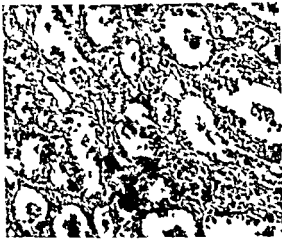
Atypical area in Brenner tumor of ovary Cells grow in solid masses and do not form "Walthard" or paramalpighian aggregates.

infoldings of the ovarian epithelial covering, to bits of tubal epithelium implanted upon its surface, or to the development of remnants of müllerian duct included in the ovary; the matter is not yet definitely settled.

Serous Papillary Adenocarcinoma. The malignant analogue of the preceding tumor is called "sero-anaplastic carcinoma" in Barzilai's classification on the grounds that it is better to indicate its histogenetic rather than its histologic type. The objection to this term is that "anaplastic" means a regression to the embryonal type on the part of an adult cell, and while the cells of this tumor undoubtedly become dedifferentiated and possibly anaplastic, they are quite as

before a definite diagnosis can be made. When the papillary growth is very marked, or when the tumor takes on a solid form (as is often the case) the gross diagnosis is easier. The growth is almost invariably bilateral; if it is not found to be so at operation there is always a chance that the contralateral organ will eventually be involved. The tumor may spread throughout the pelvis by breaking out through the capsule or by lymphatic infiltration. There is no need to describe the variations of the epithelium as observed microscopically; the histology of the tumor is, in the main, that of a non-malignant cystoma, but the cells show varying degrees of metaplasia until a point is reached at which they are best described as

pose this tumor. It is rated as rare, and its incidence is unilateral in two thirds of the cases, bilateral in the rest. Again (as in the case of serous carcinoma and serous cystoma) it merely exaggerates the features of its nonmalignant relative, the pseudomucinous adenoma. There is no need to elaborate further on its morphology or histology, the essential thing is to understand that the tumor shows exactly what might



"Mesonephroma ovarii"—a tumor of disputed origin probably resulting from shifted mesonephric elements. Note balloon like cells that project into acini and tubules on small pedicles, these are typical.

be expected in a pseudomucinous adenoma that has become malignant.

Mesonephroma This was given the above name by Schiller in 1939, so that its establishment as an entity is recent. Up to that time it was just another seropapillary ovarian tumor. It is usually small and macroscopically undistinguished. Microscopically it is composed of multiacinar adenomatous complexes lined by very low cells that resemble endothelium and occasionally take on a form in which they project into the glandular lumina in the shape of swollen spheroids attached to the basal membrane by narrow processes. Thus they are kite-shaped. Here and there they are grouped into structures that resemble the glomeruli of the mesonephros. Schiller postulates that bits of that organ become included in the

ovarian primordium when this is still adjacent to that primitive organ, his diagrams and photomicrographs are very convincing, but there is still hesitancy on the part of some pathologists to accept his thesis. As a counterproposal, gynecologic pathologists call this an "embryonal carcinoma" and link it up with the dysgerminomas. The tumor may have malignant varieties, but usually it is innocent, which limits the term "carcinoma" to the malignant type only, leaving the nonmalignant one nameless.

Schiller was strongly influenced by the resemblance of the glomeruloid structures to mesonephric glomeruli and at the same time to abortive glomeruloid structures noted in embryonal renal tumors (Ewing's "tumors of the renal blastema") which are occasionally encountered and show a distinct similarity to these ovarian new growths.

GROUP 7 Secondary Carcinoma of the Ovary Carcinomas in the breast, suprarenal, and some other organs may metastasize occasionally to the ovary, carcinomas of the alimentary tract often do so, and those of the stomach that produce many signet ring cells also produce the Krukenberg tumor with unpleasant regularity. Krukenberg originally described this form of metastasis in connection with gastric carcinoma, it is improper to call the metastasis of any other carcinoma of the alimentary tract a "Krukenberg tumor," although very similar ovarian metastases may be sired by carcinomas of the intestine. Grossly, the ovary becomes much enlarged, firm, and fibrous. The tumor may be unilateral or bilateral, usually the latter. There is little need for a lengthy description beyond mentioning the fact that such growths may attain a diameter of 25 cm. or so and resemble a medicine ball in their appearance and texture.

It may be hard to diagnose the growth under the microscope, as the signet ring cells may be relatively few in number and inconspicuous. Their presence appears to stimulate a tremendous desmoplastic reaction that causes the ovarian stroma to grow



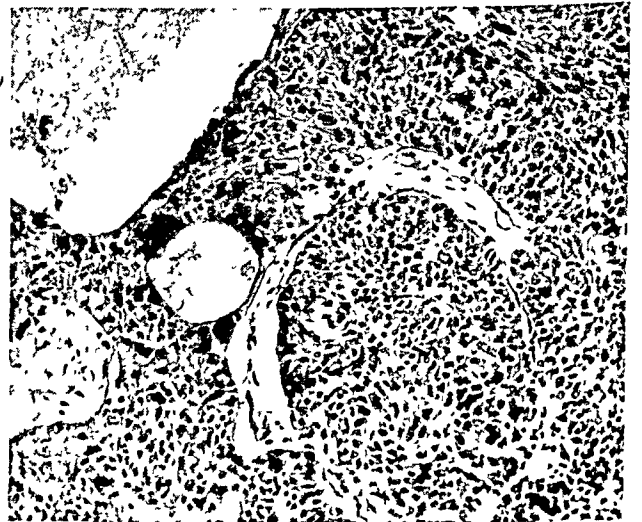
This field includes two pseudomucinous cysts from cystadenoma of ovary. Note excellent differentiation of their epithelium and its resemblance to that of uterine cervix.

saded about a dedifferentiated core of fusiform cells, may indicate a relationship between the two.

Like the serous adenoma, the pseudomucinous adenoma may rupture spontaneously or during operative procedure, with a resulting seeding out of small daughter tumors all over the peritoneal surface. Instead of provoking ascites, however, these secrete mucus-like material. Most of the historical gigantic tumors of the ovary so frequently reported in the literature of the medical missionaries in China are of this type; it produces the "facies ovarica," somewhat similar to the hippocratic facies of cirrhosis.

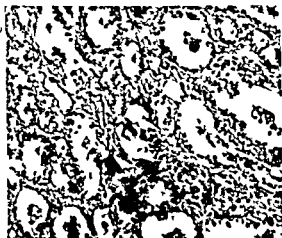
Pseudomyxoma of Ovary and Peritoneum. Barzilai differentiates this type from the preceding on the basis that it tends to rupture spontaneously and, more importantly, takes "self-evident origin" from the intestinal mucosa, rather than the müllerian or wolffian tissue. The macro- and microscopic pictures of this subvariety are not different from that of the pseudomucinous adenoma.

Pseudomucinous Adenocarcinoma. This is the malignant analogue of the two preceding forms of ovarian tumor; like the serous adenocarcinoma it represents a malignant transformation of the epithelium lining the cysts and comprised of the glands that com-



In pseudomucinous cystadenocarcinoma of ovary there are often solid areas, from one of which this section was taken. Cells are poorly differentiated, and there are small cystic cavities among them.

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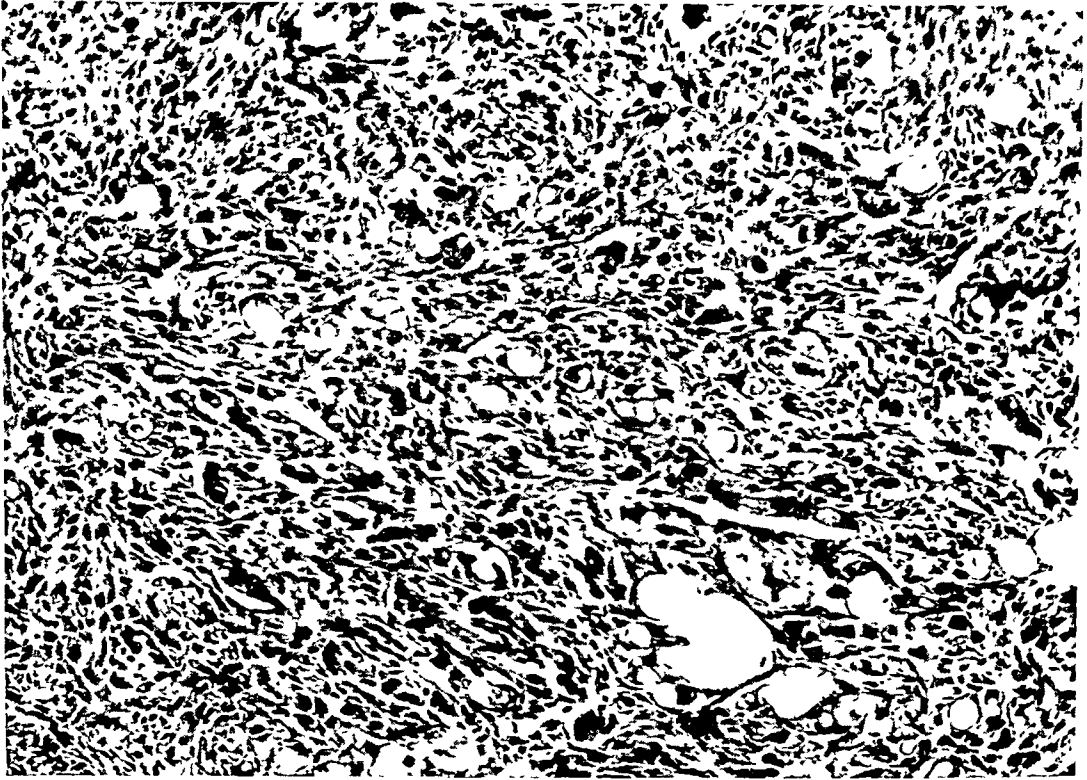
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rapidly and, in some instances, to assume sarcomatous (fibrosarcomatous or myxosarcomatous) characteristics. Here and there throughout the welter of collagenous fibers one may find nests of rather small, inconspicuous cells containing large vacuoles filled with mucus and resembling signet rings. In other instances the growth of these

ter tumors undergo spontaneous regression. If these proceed as metastases from the malignant varieties of such tumors, however, it is better to resort to x-ray treatment of the peritoneal cavity, for no such regression can be expected in the malignant new growths; their surgical extirpation is impossible after the peritoneum has been in-



Krukenberg tumor of ovary which is merely a characteristic ovarian metastasis of a gastric carcinoma which provokes a lively overgrowth of connective tissue in the organ. Note vacuolated "signet-ring" cells of gastric tumor.

cells may be more vigorous and may almost dominate the picture. The clinical history of an antecedent gastric lesion is very important in connection with diagnosis. It has happened that a woman, having been examined roentgenologically and reported as presenting a pyloric defect interpreted as carcinoma, has had two enormous Krukenberg tumors removed at separate operations before the surgeon examined the stomach at a laparotomy.

TREATMENT OF OVARIAN TUMORS. Almost invariably operative surgery is the best method of treatment of ovarian tumors. After removal of some of the tumors that tend to seed themselves out, like the serous and pseudomucinous adenomas, the daugh-

tered tumors undergo spontaneous regression. Surgical removal is the treatment of choice in most instances; this may be combined with x-ray therapy, as already outlined, or in connection with the dysgerminomas.

The high hopes that were once entertained in connection with x-ray treatment have been considerably dampened with the passing of time, for results have not corresponded to anticipation. Irradiation, if it does not make the patient too ill (as so often happens) may exert considerable psychological benefit, but its direct results may be disappointing. The late fibroses that develop as a consequence of irradiation in the course of five or more years after treatment are only just beginning to come to light.

Intestinal fibrosis may lead to obstruction and a kind of fibrotic regional enteritis. Surgery still seems to be the best and safest treatment.

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TECHNIC AND INTERPRETATION OF VAGINAL SMEARS

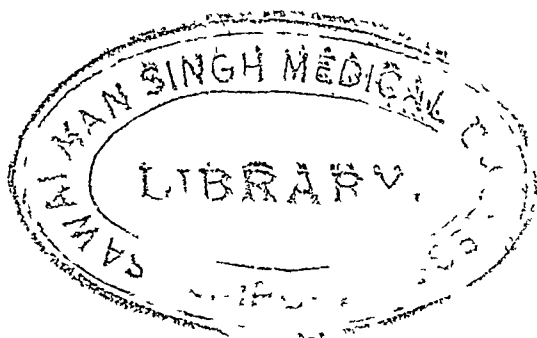
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19

Breast

DEVELOPMENT, PHYSIOLOGY, HISTOLOGY

CONGENITAL ANOMALIES

HYPERTROPHY

INFLAMMATION

CYSTS

CHRONIC FIBROCYSTIC DISEASE

TUMORS

OF NIPPLE

OF DUCTS

TUMORS (Continued)

OF CANALICULI

OF ACINI

RETICULUM CELLED SARCOMA

IN MALES

OF ACCESSORY MAMMARY TISSUE

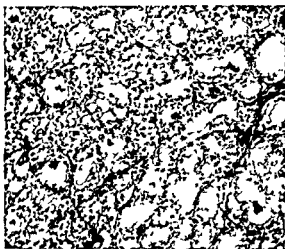
GENERAL CONSIDERATION OF CANCER OF THE BREAST

Development, Physiology, Histology

These organs develop from the skin very much in the manner of a sweat gland, particularly one of the apocrine variety. They are, therefore, very much modified sweat glands, but that they contain true sudoriferous tissue, as has been maintained by Lee, Pack, and Scharnagel and other representatives of the Memorial Hospital group in New York, cannot be confirmed by consultation with histologists or by considerable reference to the larger systems of histology, such as that of Hencke and Lubarsch.

The mammary gland consists of a tree of ducts, beginning in multiple, straight trunks in the nipple, these branch and pass through an intermediate phase in which the lining epithelium may closely resemble that of a sudoriferous duct. These, in turn, split up into innumerable canaliculi, at the end of which are clusters of acini. Thus the general arrangement somewhat parallels that of the bronchial tree but the "trunk" is not a single tube but a compact group of them. During menstruation and shortly before and after this period the acini are evident in the midphase between periods they may be difficult or impossible to recognize. Rosenberg led the way in demonstrating this. In such a resting state the

mammary gland takes on the appearance of that of the male, which seldom if ever exhibits acini. During pregnancy and lactation the acini become very evident, consti-



Normal lactating mammary gland. Note vacuolization of acinar cells. This section is often mistaken by students for carcinoma.

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19

Breast

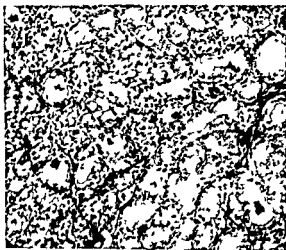
DEVELOPMENT, PHYSIOLOGY, HISTOLOGY
 CONGENITAL ANOMALIES
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 INFLAMMATION
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 CHRONIC FIBROCYSTIC DISEASE
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TUMORS (*Continued*)
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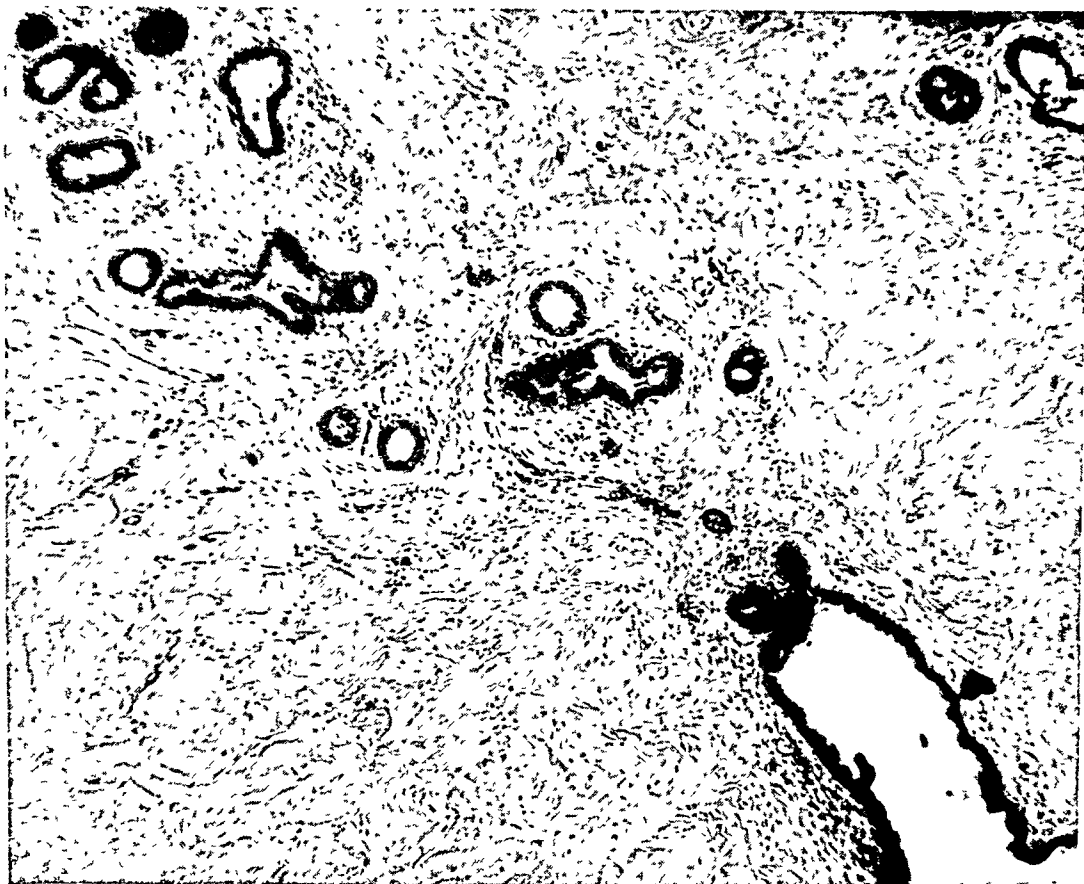
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The gland as a whole is a semiconvex, discoid mass of firm white tissue, always very fibrous, that underlies the nipple which crowns its center, around it is a large

amount of fat which varies in amount with the type of individual. Very often the plumper breasts are less well supplied with glandular tissue than are those that exhibit a more moderately fatty panniculus. The organ is readily traumatized on account of its unsubstantial, fatty make-up and its ex-

a mammary carcinoma, and second because it may constitute the source of a tumor that may develop quite independently of the breast proper. Such axillary mammary glands may attain a few centimeters in diameter; they may possess independent nipples and secrete milk during lactation.



Field from male breast showing "gynecomastia." Most sections from this lesion resemble this one closely. Note multiplication of ducts and absence of true mammary lobules which characterize female breast.

posed position. It should be remembered that a normal young mammary gland is extremely fibrous, and one should be slow in diagnosing fibrosis unless thoroughly cognizant with this fact and possessed of reliable standards.

Congenital Anomalies. Absence of the mammary gland or its nipple, as well as the occurrence of multiple nipples along the fetal "milk line" which extends from the axilla to the groin, do not interest us very closely, but the development of axillary mammary tissue is of surgical importance, first because such a development may be mistaken for a tumor or a metastasis from

Similar organs in the groin are much more uncommon.

Hypertrophy. The huge, gourd-like hypertrophied breast is often partially removed by plastic surgeons on account of its unsightliness and its weight, as well as the dragging discomfort that it occasions. Such a breast will show a very hypertrophic and fibrous mammary gland in which there may be considerable cystic degeneration and even retention cysts. There is much too much mammary tissue, but it is evenly distributed over a wide area, and its components are separated by fibrous and fatty tissue.

GYNECOMASTIA Hypertrophy of the male breast is unusual, fibrocystic disease may simulate it, and many needless operations are carried out for this condition. When it occurs in connection with certain tumors of the testis (choriocarcinoma) and endocrine disturbances it is genuine, but even so this does not indicate its removal, rather

effects of abscess, scars may develop, or the contents may liquefy and form a pseudocyst with leathery walls so hard that the spherical mass may be mistaken for carcinoma.

CHRONIC MASTITIS As a continuation of acute mastitis and, as a rule, a consequence of retention of secretion, there may be chronic inflammation of the gland that man-



Chronic mastitis of lymphocytic type (relatively unusual). These cells are infiltrating the periductile and pericanalicular stroma.

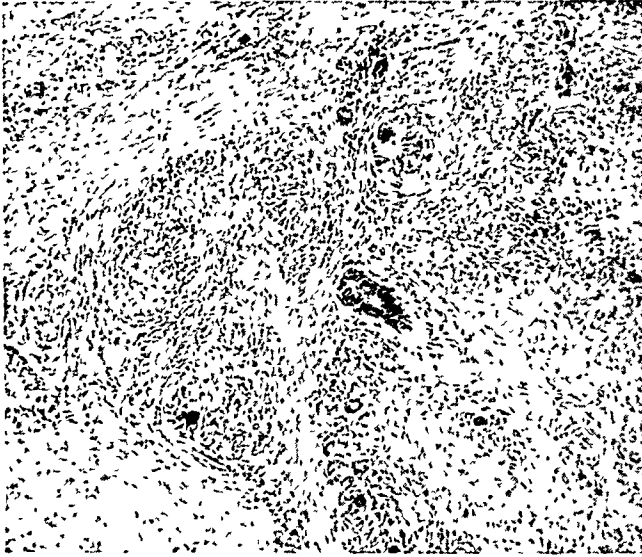
it points toward removal of the testicular tumor or to endocrine therapy. Such hypertrophied male breasts may secrete colostrum, as they do during the transient hypertrophy of infancy and adolescence, but one seldom if ever finds acini in them.

Inflammation ACUTE MASTITIS The most important acute inflammations of the mammary gland follow infection during lactation, when organisms find entrance through cracks and abrasions in the nipples. The acute phases of mastitis that precede suppuration and abscess formation do not concern us here. Occasionally abscesses fail to heal and bits of abscess wall are submitted to the pathologist for examination. Unless the infection is specific, nothing much more than the usual signs of acute inflammation are forthcoming. As after-

manifests itself as a nodular, rather painful breast simulating that of chronic fibrocystic disease, it is only under the microscope that the difference is evident. There are two main microscopic varieties: (1) a diffuse infiltration by lymphocytes with a concomitant fibrosis and production of cystic dilatation of the ducts and canaliculi, which constitutes true chronic cystic mastitis, and (2) a form in which there are granulomas comprising not only lymphocytes and plasma cells, but collections of foreign body giant cells that may simulate specific tubercles. This latter is not a type that has attracted universal notice, and only a few pathologists (notably Frank Mallory) have stressed it.

CHRONIC INFLAMMATION OF BREAST Another type of chronic inflammation is resident in the fat that surrounds the gland.

this may follow trauma or inflammation, or it may occur in connection with febrile panniculitis, which causes widespread fat



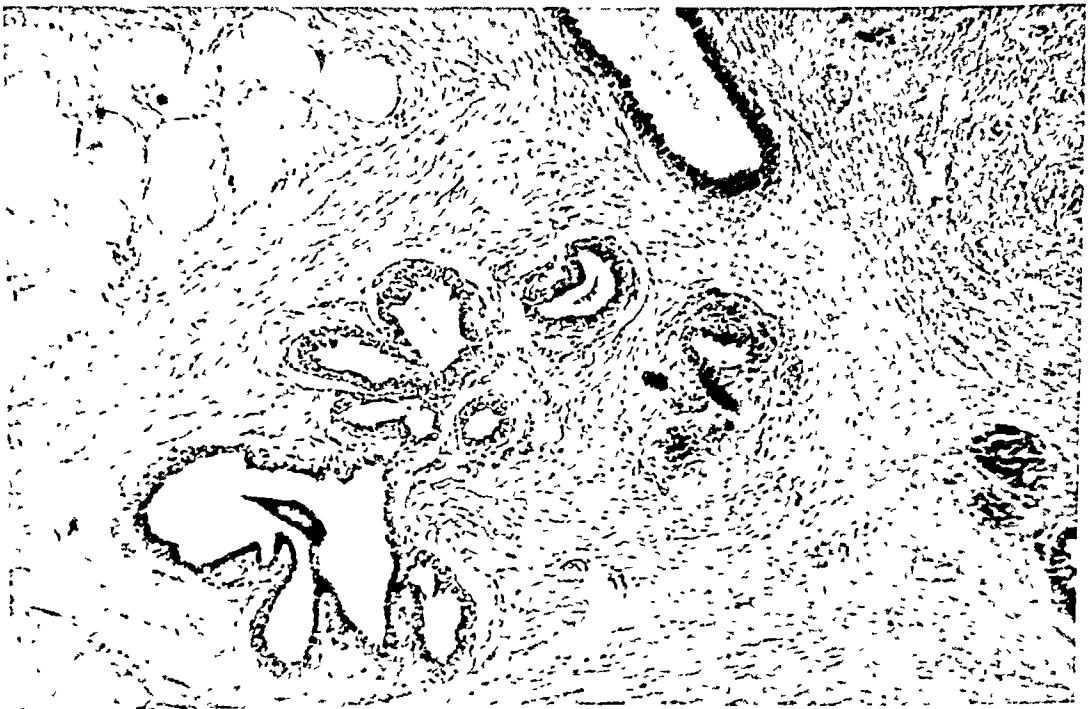
Field from area of tuberculous mastitis. A small duct is seen at center of field. Lesion is fibrous rather than caseous in this instance.

necroses in the panniculus adiposus. Shotty areas may be felt in the breast which, on exposure, show up as hard, yellowish, soapy areas of fatty necrosis from a few millimeters to a centimeter or so in diameter. (These are fully considered in Chapter 7

under Trauma and Inflammation of Adipose Tissue.)

INFECTIOUS GRANULOMA. Of the varieties of specific infectious granuloma, tuberculosis is not at all common, in spite of the fact that it is notoriously so in the cow's udder. It may take five forms (according to Deaver and McFarland, quoted by Karsner): miliary, conglomerate, sclerosing, obliterating, and miscellaneous forms grouped as "atypical." Many cases of "tuberculous mastitis" will, on careful review of the sections, prove to be the retention type of chronic mastitis that forms pseudotubercles. Syphilis and actinomycosis are seldom matters for surgical pathologic attention, although biopsies may be submitted from cases suspected of being actinomycotic.

Cysts. GALACTOCELE. This is a form of retention cyst observed in connection with obstruction of the larger lacteal ducts; as a rule it follows discontinuance of nursing. The cyst contains milk or colostrum which is creamy, it is lined by a thinned-out epithelium of the ductile type, and there may be a history of mastitis as well as of lactation. Occasionally the contents become fairly inspissated and cheesy.



Dilated and fibrotic lacteal ducts in chronic fibrocystic disease of breast. Further dilatation would lead to production of "blue-domed cysts."

SIMPLE OR "BLUE DOMED" CYST This is also a retention cyst, but its contents are watery and brownish to bluish green in color, instead of being colorless, as usually described (See color plate of blue domed cysts) The cysts vary in size from a few millimeters to one or more centimeters, rarely being over 4 cm in diameter They

extensively studied in sections of entire glands by Cheatle and Cutler, who discuss it voluminously in a book devoted to tumors of the breast Lacassagne has attributed the condition to a stimulation of mammary tissue by estrogen and has experimentally produced similar changes in the mammary glands of castrated male animals by the in



Well developed fibrocystic disease of usual type. A large microcyst is evident in upper right corner. Walls of blue domed cysts often have appearance of this section.

may arise singly, but as they are part of fibrocystic disease (described below) they may be multiple. They are spheroidal, but sometimes they may be elongated and blimp like. Microscopically they are seen to have fibrous walls with a thin layer of degenerated ductile epithelium for a lining. The wall may be thick and fibrous, but usually it is translucent and thin. When they are cut down upon at operation they appear like the blue domes for which they are named.

Chronic Fibrocystic Disease This is a very frequently noted affection that has been

section of that substance at regular intervals spaced over some period of time. McFarland notes that the changes one sees are all to be observed in the course of normal involution of the gland, but in the case of fibrocystic disease these are intensified. Cheatle and Cutler recognize a series of alterations in the architecture of such breasts that run a gamut from simple hyperplasia (mastoplasia), through desquamative and more extensive lesions (cystophorous desquamative hyperplasia) to the quasineoplastic condition known as "Schimmelbusch's disease" in which there is still further intensification

of cyst formation and desquamation, the formation of intraductile papillomas, and even metaplasia of the mammary tissue, which becomes almost carcinomatous and leads over by easy transitions into "carcinoma in situ," which will be discussed presently.

Breasts afflicted with these changes become "lumpy" or "weedy" and nodular, and

is a further development of papillary overgrowth of the epithelium of the intermediate and larger ducts, the former showing marked thickening and swelling, and developing a more marked eosinophilia than that which it already possesses. In these ducts one may note papillae of dense, eosinophilic cells that project like fronds into the lumen. Small, solid tumors of these cells sometimes accom-



Field from lesion of Schimmelbusch type of fibrocystic disease. Note papillary proliferation of epithelium of intermediate ducts.

as they often contain very hard nodules they are often explored, and biopsies are taken for diagnosis. That the Schimmelbusch type of fibrocystic disease may and probably does lead to carcinoma is generally believed.

In mazoplasia there is a simple overgrowth of mammary tissue; the cells are swollen and edematous so that the glands seem larger than usual. In the desquamative phase the cells peel off into the acinar and canalicular lumina; fibrosis is moderate in the early stages, but it increases steadily as the process continues. This leads to the formation of cysts, some of them small and of the microscopic variety, others large and visible to the naked eye as blue-domed cysts.

In the Schimmelbusch type of lesion there

pany the lesion. The glands become dilated and their epithelium swollen, often hyperchromatic, and even metaplastic. The intermediate ducts come to resemble those of sudoriferous adenomas, even to a hypertrophy of their myo-epithelium and the small leiomyocytes in the outer layer of their wall.

Thus, Schimmelbusch's disease straddles the line between involutional and neoplastic changes. The stroma of the mammary gland may show considerable lymphoid infiltration, but this is sufficiently inconspicuous to constitute a point in the differential diagnosis between chronic mastitis and chronic fibrocystic disease. A somewhat infrequent variant of the latter is the addition of nu-

merous small areas that so closely resemble intracanalicular adenofibromas that they might be mistaken for them, this is known as "diffuse fibrosing adenomatosis", it adds little to the prognosis of fibrocystic disease one way or the other

TUMORS OF THE BREAST

In the diagnosis of these tumors the surgical pathologist is very useful. In the opin-

quires further investigation. In such cases an aspiration biopsy would succeed no better.

In classifying mammary tumors it will be best to follow a scheme based upon the histology of the organ, but it should be borne in mind that the more one becomes familiar with tumors of the breast the more is one impressed with the futility of attempting to classify them by any hard and fast



Topographic view of a focus of Schimmelbusch type of fibrocystic disease of breast. Note cysts and overgrowth of epithelium in medium sized ducts.

ion of the writer, it has always seemed better to prepare a patient for operation, obtain a signed permit for radical operation, and then cut down upon the tumor and remove a generous biopsy (if not the entire growth) than to putter with aspiration biopsies. Should the freezing microtome produce sections that reveal cancer, the operation for radical mastectomy may then be undertaken without further delay, should a nonmalignant growth be diagnosed, the wound is then closed up forthwith and the patient returned to her bed. Seldom, if ever, is it necessary to await the examination of permanent sections from paraffin blocks, although once in a great while a frozen section may give equivocal evidence that re-

scheme, some will show the characteristics of almost every category of the classification in some part or other of one section. Furthermore, one is never satisfied that tumors presenting the appearance of canalicular origin actually arose in canaliculi, it is merely convenient to group them according to the mammary elements which they most closely resemble, as a means of systematically covering the subject. It is true that various types in a classification have various clinical characteristics and offer a variety of prognoses according to these types. We may at once dismiss from this discussion those tumors that arise not from the mammary gland, but from other tissues that compose the breast as a whole, they are

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discussed elsewhere under the subjects of connective tissue, skin, muscle, vascular structures, and so on

Tumors of the Nipple **ADENOMA OF SWEAT GLAND** Montgomery's tubercles of the areola are apocrine sweat glands and may develop adenomas that are nonmalignant growths of small size, situated at the rim of the areola. These growths may occasionally develop into "sweat gland carcinomas" that may attain considerable size. In either case, the type of the tumor is usually recognized under the microscope as having a topography and histology more in accord with that of a sudoriferous than of a mammary gland. These tumors will be discussed at length in the section devoted to the pathology of the skin; they are very confusing, as they are seldom recognized until removed and examined microscopically.

PAGET'S DISEASE OF THE NIPPLE This occurs in the skin as well as in the areola of the nipple, but it is more commonly seen in the latter. It first appears as an apparently eczematous lesion of the nipple that persists obstinately and does not yield to treatment, at first a brownish, slightly excoriated and shallow area of ulceration, it becomes more and more scaling and fibrous until the entire nipple may be transformed into a puckered brownish patch that no longer resembles a nipple at all.

Under the microscope one notes a characteristic change in the basal layer of the epidermis: there are numerous large, vesicular cells ("Paget cells") present which may show multinucleation and which are intercalated amongst the more normal elements of the basal layer. The prickly cells of the midzone become loosened and edematous, and those of the rete cones show disorganization and may wander away into the underlying tissue. This lends to the microscopic picture the appearance of a tissue that has been macerated. Not only is the epidermis changed in appearance, but similar alterations appear in the epithelium of the larger lacteal ducts, which take on the

appearance of duct cell carcinoma. There is considerable doubt as to which process initiates the lesion, that in the epidermis or that in the ducts. Early lesions, which seldom come under observation, appear to indicate that the process begins in the epidermis and invades the ducts by extension. Muir discusses this phase of the subject at length. This is a disease of later life, it is noted between the ages of 40 and 60 and appears to be a true, malignant neoplasm—hence a carcinoma that should be energetically dealt with.

Tumors Originating in Cells of Ducts **NONCANCEROUS GROUP** *Simple Adenoma* Small adenomatous tumors may develop in the ducts and occasion lumps that call for surgical intervention; they cannot be satisfactorily diagnosed without recourse to the microscope. They may be composed of solid masses of cells resembling those of the epithelium of the duct ("comedo adenomas" of Bloodgood) or they may be multiacinar, reminding one of certain prostatic carcinomas, although they are not, like those, malignant. They are frequently seen in connection with the Schimmelbusch type of fibrocystic disease.

Papillary Adenoma Instead of forming solid or multiacinar adenomas, the duct cells may grow out in a papillary fashion and invade the lumen with a reddish, polypoid complex of frond-like papillae which are usually of the "true" type, being possessed of a delicate vascular stroma. These tumors may be only a few millimeters in diameter, but as they have this vascular stroma and the papillae are very fragile, they readily become traumatized and bleed. Thus bleeding from the nipple usually means that a "duct papilloma" is present. Occasionally they undergo malignant transformation.

Papillary Cystoma This tumor resembles the preceding one, but lies deeper and presents a different microscopic picture. The duct is dilated into a cyst, from the walls of which spring numbers of coarse pseudo-papillae which have no stroma and present a distinct affinity for acid dyes. This tumor,



One field exhibiting at the same time: (a) fibrocystic disease, (b) intraductile adenoma, and (c) scirrhous carcinoma. The last may be noted as a scattering of cells in lower right corner, a few being present also in lower left. This illustrates inadvisability of too rigid classification of mammary tumors.



Epidermal lesion in nipple as a result of Paget's disease. Note large vesicular cells in rete and general disruption of epidermal pattern.

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Tumors Originating in Cells of Ducts **NONCANCEROUS GROUP** *Simple Adenoma* Small adenomatous tumors may develop in the ducts and occasion lumps that call for surgical intervention; they cannot be satisfactorily diagnosed without recourse to the microscope. They may be composed of solid masses of cells resembling those of the epithelium of the duct ("comedo adenomas" of Bloodgood) or they may be multiacinar, reminding one of certain prostatic carcinomas, although they are not, like those, malignant. They are frequently seen in connection with the Schimmelbusch type of fibrocystic disease.

Papillary Adenoma Instead of forming solid or multiacinar adenomas, the duct cells may grow out in a papillary fashion and invade the lumen with a reddish, polypoid complex of frond like papillae which are usually of the "true" type, being possessed of a delicate vascular stroma. These tumors may be only a few millimeters in diameter, but as they have this vascular stroma and the papillae are very fragile, they readily become traumatized and bleed. Thus bleeding from the nipple usually means that a "duct papilloma" is present. Occasionally they undergo malignant transformation.

Papillary Cystoma This tumor resembles the preceding one, but lies deeper and presents a different microscopic picture. The duct is dilated into a cyst, from the walls of which spring numbers of coarse pseudo papillae which have no stroma and present a distinct affinity for acid dyes. This tumor,



One field exhibiting at the same time: (a) fibrocystic disease, (b) intraductile adenoma, and (c) scirrhous carcinoma. The last may be noted as a scattering of cells in lower right corner, a few being present also in lower left. This illustrates inadvisability of too rigid classification of mammary tumors.



Epidermal lesion in nipple as a result of Paget's disease. Note large vesicular cells in rete and general disruption of epidermal pattern.

discussed elsewhere under the subjects of connective tissue, skin, muscle, vascular structures, and so on

Tumors of the Nipple **ADENOMA OF SWEAT GLAND** Montgomery's tubercles of the areola are apocrine sweat glands and may develop adenomas that are nonmalignant growths of small size, situated at the rim of the areola. These growths may occasionally develop into "sweat gland carcinomas" that may attain considerable size. In either case, the type of the tumor is usually recognized under the microscope as having a topography and histology more in accord with that of a sudoriferous than of a mammary gland. These tumors will be discussed at length in the section devoted to the pathology of the skin; they are very confusing, as they are seldom recognized until removed and examined microscopically.

PAGET'S DISEASE OF THE NIPPLE This occurs in the skin as well as in the areola of the nipple, but it is more commonly seen in the latter. It first appears as an apparently eczematous lesion of the nipple that persists obstinately and does not yield to treatment, at first a brownish, slightly excoriated and shallow area of ulceration, it becomes more and more scaling and fibrous until the entire nipple may be transformed into a puckered brownish patch that no longer resembles a nipple at all.

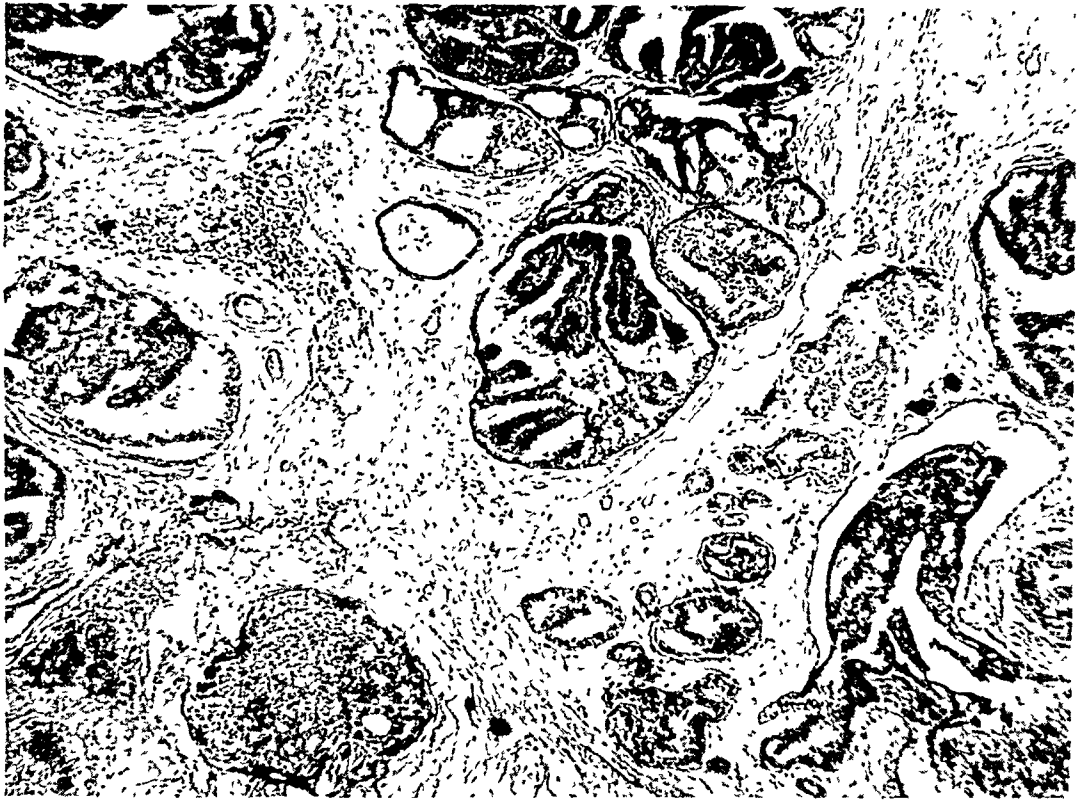
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Area of multiple intraductile adenomas and papillary adenomas of larger mammary ducts. This is often seen in connection with Schimmelbusch type of fibrocystic disease of breast.

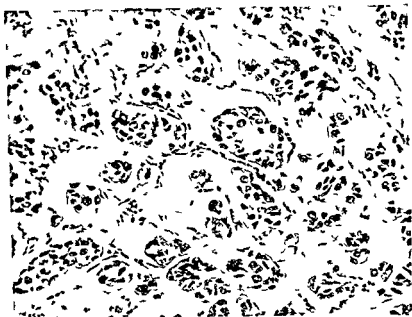


Duct-celled or "comedo" carcinoma of mammary gland. The larger masses of cells will ultimately break down centrally, producing necrotic casts which gave tumor the name "comedocarcinoma."

too, is often seen in Schimmelbusch's disease. That the tumor may become malignant on occasion is indicated by the appearance of eosinophilic papillary areas in mammary carcinomas.

CANCEROUS GROUP SIMPLE "DUCT CELLED" CARCINOMA These growths are divisible into three microscopic types, grossly observed they are stone hard tumors in the proximity

except that they manifest metaplasia and a few mitotic figures. If this were all, they might pass as slightly metaplastic "comedo adenomas" and could be safely treated by simple mastectomy, unfortunately they are usually accompanied by a scirrhous form of small celled carcinoma that invades their stroma. Bloodgood believed that this represented a combination of two tumors, com-



Tubular and more malignant variety of duct celled carcinoma of mammary gland. Some areas of this tumor showed solid or "comedocarcinomatous" type of growth, which is less malignant. Most of this tumor, however, is of the tubular variety.

of the nipple where the large ducts converge, and they may or may not show infiltrative tendencies. Those that are known as "comedocarcinomas" are characterized by the appearance of cylindrical casts like paint from a tube when they are subjected to pressure. Bloodgood likened these to the sebaceous plugs that one may express from obstructed sebaceous ducts on the nose or face—the familiar "blackheads," known as "comedones" in professional circles.

Solid Type The microscope reveals this type to be composed of solid cylindrical masses of slightly metaplastic cells from the epithelium of the ducts which completely fill their lumina, thus they have the same architecture as that of the solid adenomas

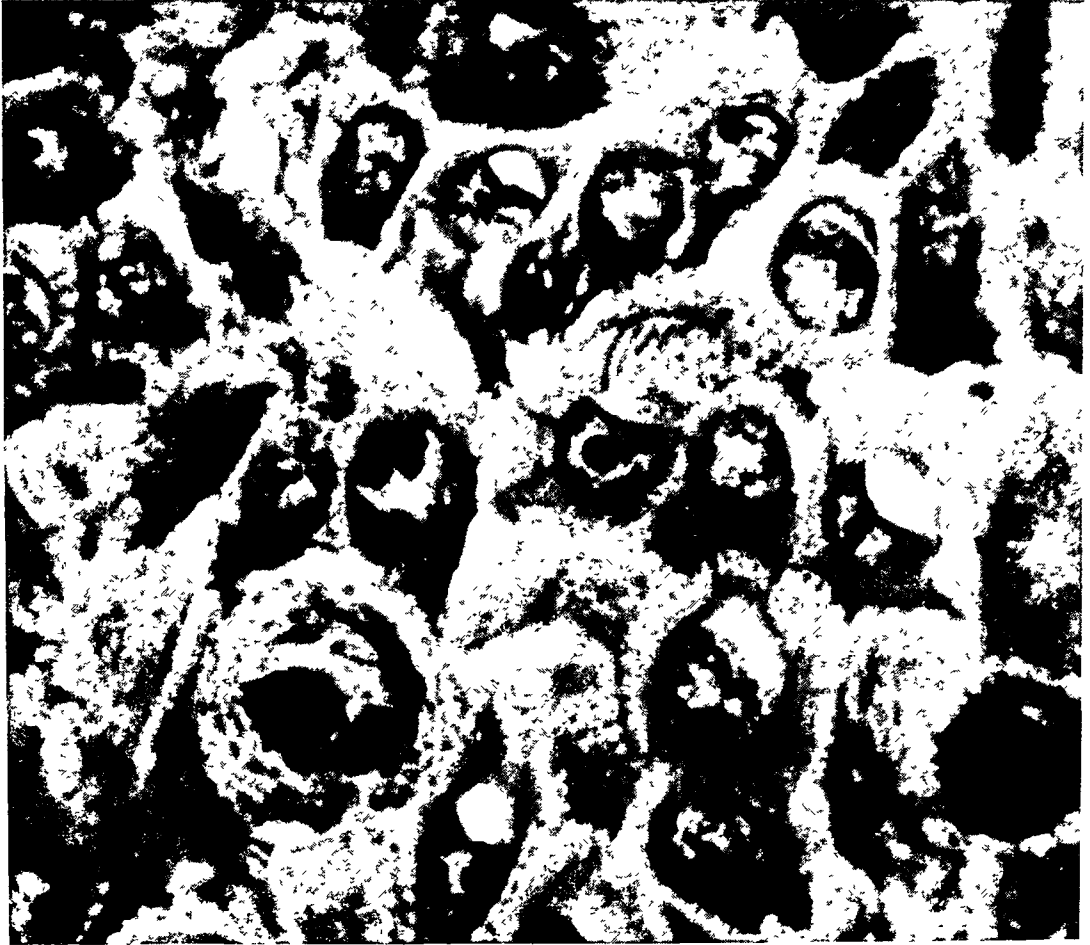
and comedo adenoma and scirrhous carcinoma, but it is so often observed that it is best to consider that both elements are part of the same neoplastic process. It is quite possible that some of the cells from the ducts escape into the stroma and there set up the scirrhous type of growth. These tumors carry a less serious prognosis than do most mammary carcinomas, they are common in old women whose breasts usually show considerable chronic inflammatory change in their ducts in areas well away from the actual tumor. They are seldom accompanied by metastases.

Tubular Duct celled Type Here again the distinguishing characteristics are microscopic, the cells of the ducts become meta-

plastic and grow in a tubular form that invades the surrounding tissue and does not tend to become massed into the solid plugs of the comedocarcinoma.

Epidermoid Carcinoma. This develops deep in the core of the breast from a meta-

celled carcinoma." The two we have seen have been extraordinarily malignant, metastasizing early and widely and killing within a year after operation. As epidermoid metaplasia is a common sequel to chronic inflammation in the gallbladder, renal pelvis,



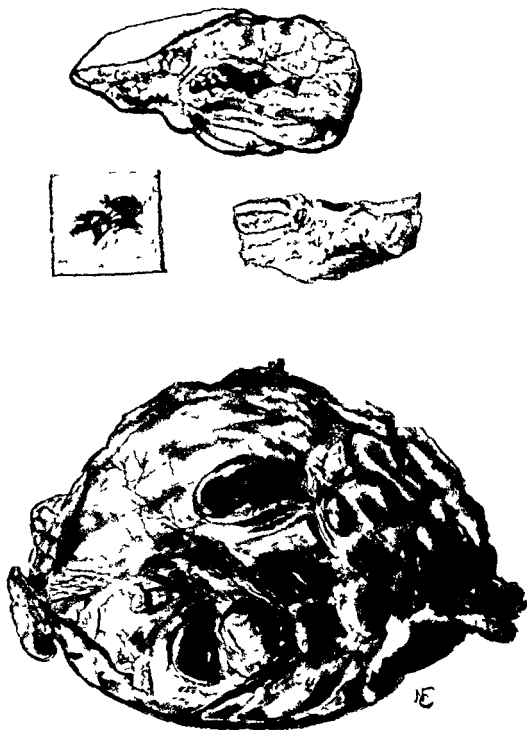
Oil-immersion photomicrograph of area of prickle-cells in a deeply situated epidermoid carcinoma of breast that was exceptionally malignant. Note intercellular bridges. Black masses are keratin. Note also that in spite of the excellent differentiation this tumor resulted fatally nine months after it was first noticed.

plasia of the ductile epithelium, or from epidermoid rests; one cannot be certain which is the more accurate interpretation. It is a distinctly rare tumor, the German literature to the contrary notwithstanding; in twelve years only two good examples have come to our laboratory from a service that is "top-heavy" in mammary tumors. Under the microscope this one is seen to be a true epidermoid carcinoma which develops all the layers of the epidermis but concentrates on the formation of prickle cells; hence it is really a malignant acanthoma or "prickle-

urinary bladder and occasionally the stomach, it is not irrational to attribute the etiology of this tumor to such metaplastic changes.

PAPILLARY DUCT-CELLED CARCINOMA. The papillary adenoma just described sometimes undergoes metaplastic changes and shows marked evidence of cellular division and a tendency to invade the wall from which it springs, spreading in the tissue about the ducts. This constitutes an adenoma malignum, and simple excision will not suffice as a curative measure; the writer has seen

PLATE VIII

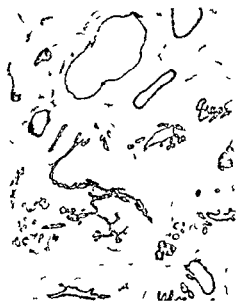


(Top) Mammary carcinomas (Above) Section through duct called carcinoma which is not particularly distinctive in its appearance (Below, left) View of surface over scirrhous carcinoma, demonstrating retracted nipple and next to this a sluggish, scabbed-over ulcer (Below, right) Sagittal section of same tumor, showing characteristic streaking of scirrhous carcinoma and its indefinite outline

(Bottom) Blue domed cysts unusually large and numerous, studding entire breast (seen from its costal surface) They are not necessarily blue, but take their color from their content and overlying tissues

such tumors continue to develop after simple excision and ultimately produce duct cell carcinomas

Canalicular Tumors of Mammary Gland NONCANCEROUS GROUP *Simple Glandular Adenoma* This tumor is well encapsulated, firm, ovoid, and light brown, it may occur anywhere in the breast, but



Field from a limited area of "diffuse fibroadenomatosis" in combination with chronic fibrocystic disease of the breast. Note the similarity to an intracanalicular adenofibroma

usually it is found in its dependent half. It may be seen in young women, as well as in the middle aged. So much does this little neoplasm resemble an accessory mammary gland that its microscopic appearance often puts the pathologist in a quandary. It is differentiated to a degree that lends it an organoid appearance, with branching ducts, acinar glands, and well ordered stroma. Cystic dilatation of its canaliculi may give rise to very bizarre pictures and make the tumor quite spongy in consistence.

Fetal Adenoma This is found in the same places as the preceding type, it is well encapsulated and usually affects girls and young women, its gross appearance is much

like that of the glandular type, but its microscopic picture is quite different. As it resembles fetal breast Ewing called it a



Simple canalicular adenoma of mammary gland. Note section that appears in some of lumina as black masses. It is deep red in original sections.

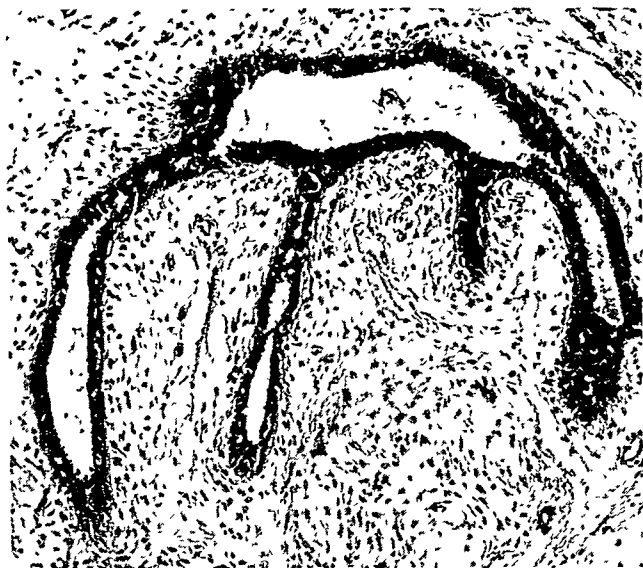


Fetal adenoma of mammary gland. Both epithelium and stroma may exhibit evidence of rapid growth and some metaplasia, but tumor is not malignant. It resembles fetal adenoma of thyroid in its microscopic appearance.

"fetal adenoma." Somewhat resembling the fetal adenoma of the thyroid, it is composed of tubules and acini comprising cuboidal epithelium and embedded in a loose, vascular, and generous stroma. Both epithelium and stroma may show numerous mitotic

figures and lead the inexperienced observer to diagnose a malignant growth, but from the practical standpoint this may be discounted; once removed in its capsule, it does not recur.

Fibro-adenoma. The fibro-adenoma has been the subject of much description, classification and discussion, all of which has probably been too elaborate. It is a non-malignant growth that is usually found in



Typical intracanalicular type of fibro-adenoma of breast. Note geographic pattern of distorted wall of canaliculus.

the lower half of the breast of nulliparae or of women who at least have not suckled a child. It is well encapsulated, firm, and elastic, and on section it is seen to be translucent and pearly white, with clefts running this way and that across a coarsely granular sectioned surface. If the clefts are abundant the tumor is probably of the intracanalicular kind; if not, it is probably of the pericanalicular variety. These distinctions amount to very little, as both types may be noted in the same growth as often as not.

Microscopically it is found to consist of a great deal of collagenous connective tissue which envelops ducts that appear to be canaliculi of the mammary gland. The fibrous tissue may be arranged in a circular fashion about these to constitute the pericanalicular type, or it may form stout and

bulbous projections that thrust into the dilated canaliculus and push its epithelial lining over their surface, where it is stretched tautly. This causes clefts that, in microscopic sections, take on a geographic outline and resemble branching inlets, bays with promontories, and whatnot. The epithelium may show little or no change from its normal state, or it may be hyperplastic and tend to form several layers and occasional mounds of cells. It may even produce intraductile papillomas—tumors within tumors. At times there may be considerable metaplasia of the epithelium of the deformed canaliculi, but this need occasion no alarm if the tumor is well encapsulated.

Cheate and Cutler describe three types: subepithelial, in which the fibrous overgrowth occurs within the elastic coat of the canaliculus; pericanalicular and periacinous, in which this lies outside of the elastica; and a third type which presents a mixture of the first two and rather nullifies their validity as strict types. There may be distinct mucoid degeneration of the stroma in these tumors, but this does not change their fundamental nature nor their favorable prognosis; it affords an opportunity for using the term “papillary intracanalicular myxofibro-adenoma,” which is at least imposing. As to which is the horse and which the cart, in the case of these tumors, it is difficult to say; that the growth-promoting stimulus may reside now in the one and again in the other is indicated by the fact that there are malignant analogues of these tumors which show sometimes carcinomatous changes in the epithelium, sometimes sarcomatous alterations in the stroma, and rarely both.

CANCEROUS GROUP. CANALICULAR CARCINOMA. The tumors of this group constitute the largest part of the cancers of the breast; in the past they have been divided into several groups. They simulate canaliculi in their structure, but whether they really arise from canaliculi and whether the subdivisions into distinct groups are justified are

problems, it is convenient to consider them as being of canalicular origin, and as canaliculi compose the bulk and constitute the most numerous elements of the mammary tree, this derivation seems the most probable. One should bear in mind, however, that mammary carcinomas may show many or almost all of the subtypes in appropriately selected sections from the primary growth and its metastases. Some of them, then, may originate in one portion of the gland while others may be more or less multicentric in origin, arising in ducts or acini as well as in canaliculi, all at the same time.

Simple Type "Carcinoma simplex" of the literature is a tumor that grossly resembles



Simple form of canalicular mammary carcinoma that developed in breast of patient from whom a lobular carcinoma in situ was locally removed two years before. This illustrates necessity for mastectomy in the case of this tumor (See page 410)

a scirrhous carcinoma, but when examined under the microscope it is more glandular and less fibrous. Thus its chief characteristics are microscopic. It is composed of cords of spheroidal or ovoid cells that do not tend to form glands, are embedded in a stroma of fibrous tissue that varies in amount and density, and show variations in their size, some tumors comprise cells about the size of lymphocytes, while others

may be composed of cells that are about twice those dimensions.

Solid Type In this, the gross appearance is more definitely suggestive of epithelium, being white and granular and grouped into tiny alveolar masses in a fibrous stroma. It was formerly called "medullary" because some of the tumors resembled bone marrow, it was also (and more appropriately) termed "alveolar." Its cells are much like those of the simple type, but instead of being grouped into cords they are massed into

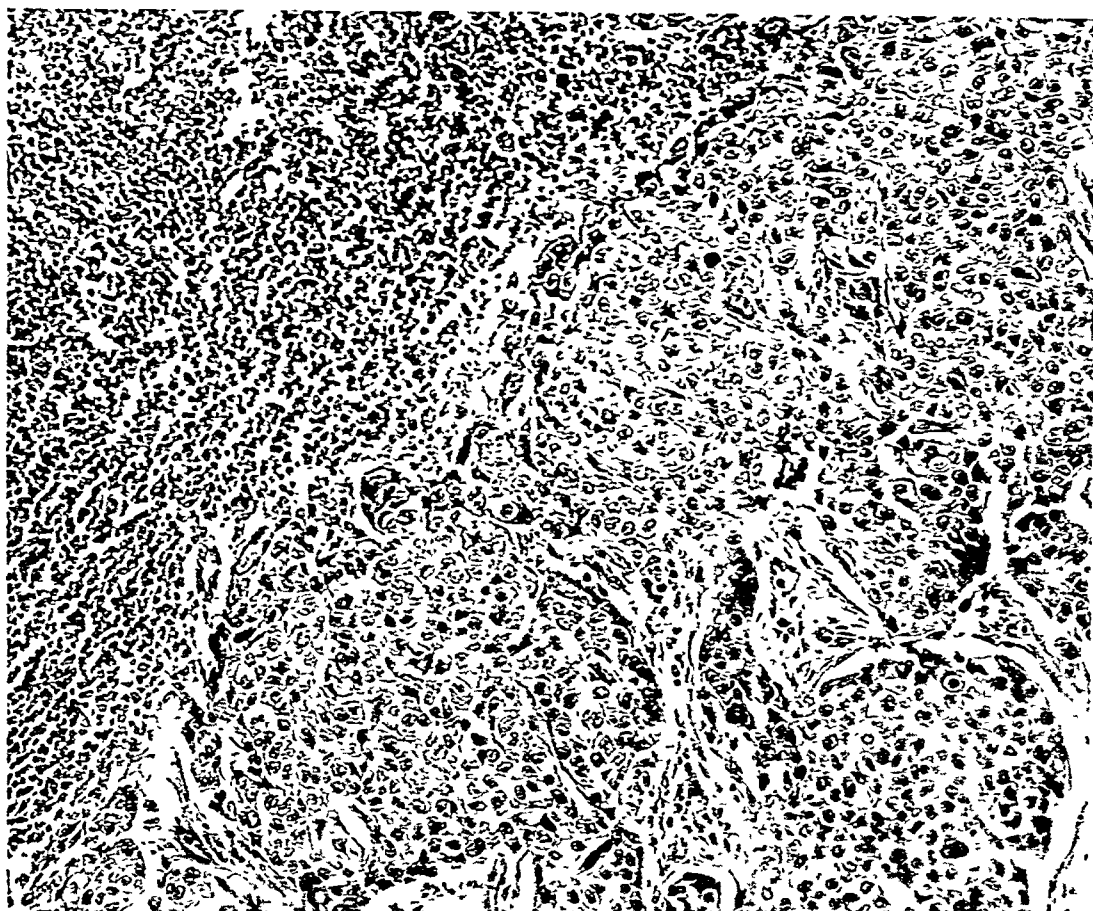


Typical solid type of canalicular carcinoma, often called "medullary"

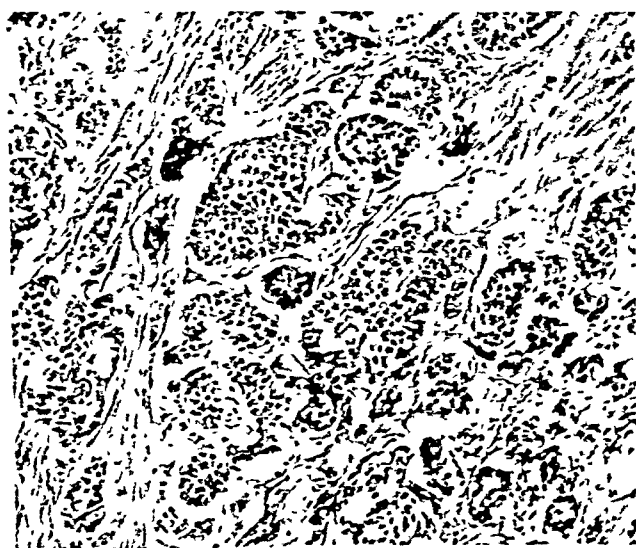
solid spheroidal or ovoid complexes. Both the simple and the scirrhous types may take on this form when they invade loose tissue or metastasize to the axillary nodes, the type seems to depend upon the density of the stroma of the neoplasm rather than upon any inherent difference in its cells.

Adenomatoid Type This is an adenocarcinoma that tends to form canaliculi and acini, grossly it is little different from the preceding forms, while under the microscope it may exhibit areas that are exactly similar to them.

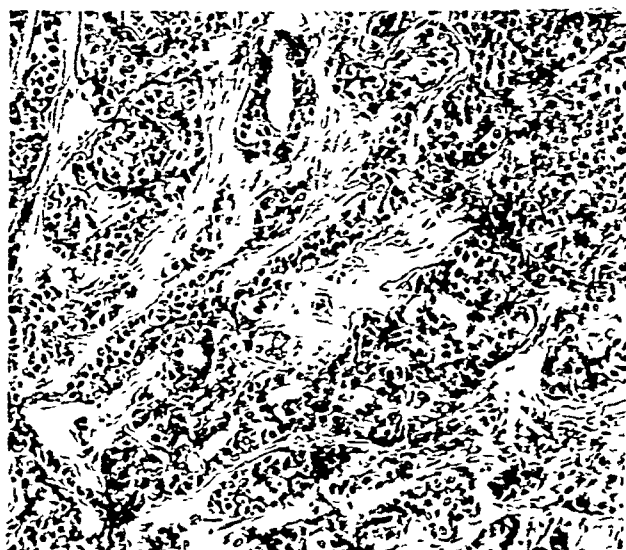
Mucous Type This is essentially a somewhat more slowly growing form of the preceding type. In the gross it looks gelatinous and tends to be somewhat circumscribed. Under the microscope it is found to differ from the adenomatoid type in that it se



Metastasis of solid type of canalicular carcinoma of breast in an axillary lymph node.



Combined solid and simple types of canalicular mammary carcinoma.



Adenomatoid type of canalicular mammary carcinoma. Note lumina formed by neoplastic cells.

PLATE IX



Kodachrome photomicrograph of mucous carcinoma of breast. Note clumps of red epithelial cells apparently suspended in blue staining mucus.

cretes large amounts of mucus which collects in the glandular spaces and may dominate the picture. Then the cells of the tumor appear in small, apparently inhibited groups that are embedded in mucus, figuratively "stewing in their own juice." When such tumors metastasize, however, they may abandon the formation of mucus and show a solid or adenoid form of growth, hence they are not to be underestimated. Frantz



Adenomatoid type of canalicular carcinoma of breast, in places tending to become more solid than adenoid

has investigated mammary tumors for the presence of mucus ("mucicarmophil material") and concludes that when it is found in one this indicates a lesser degree of malignancy. So far as we have been able to check this observation it has been strikingly well borne out. (See color plate.)

Scirrhus Type Grossly these very common carcinomas are usually about a cubic centimeter in volume, white to yellowish white in color, and wooden in consistence, they are poorly delimited and tend to send out strands and rays of neoplastic tissue into the surrounding fat. When they are cut, the edge of the incision remains sharply angular and does not tend to round off, as does that of a cut made in fibrous tissue. It is unusual, nowadays, to observe very large examples of this form, as patients have become more cancer conscious, the tumor

grows relatively slowly and is brought to the attention of the surgeon before attaining large dimensions. One seldom sees one of them that measures over 4 cm. on a side. They are almost invariably single, although there may be two or three, very exceptionally one will encounter an example showing seven or eight small tumors in one breast, scattered through its adipose tissue.

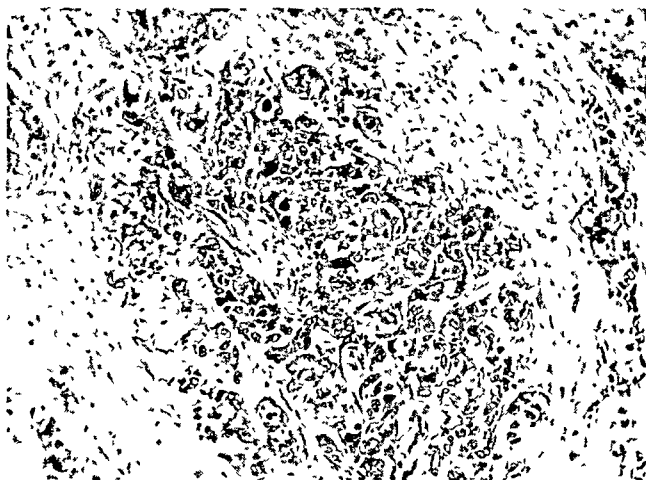
Under the microscope such growths are found to be largely composed of ligneous fibrous tissue with small cords of inconspicuous, rather well differentiated cells forming chains and groups in the stroma. This has led some observers to consider the fibrous overgrowth as a defensive mechanism, but although this may in a measure be true in the mammary gland itself, the tumors grow like wildfire in the axillary metastases, where they may provoke no similar desmoplastic reaction, although they can do so on occasions.



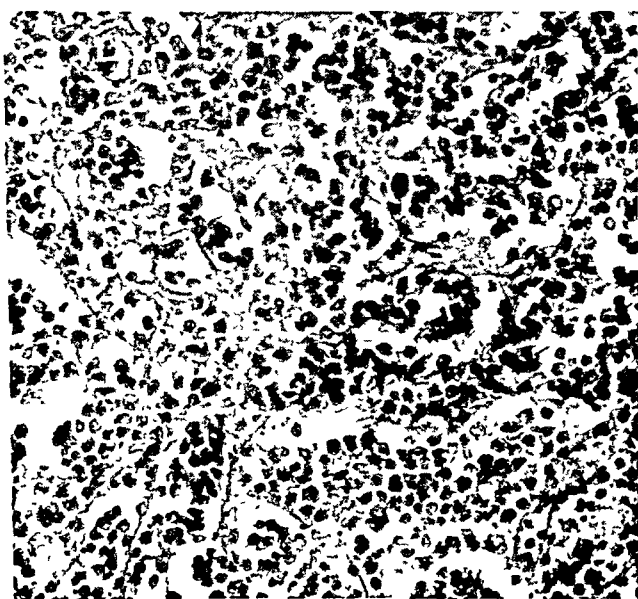
Slightly hypercellular scirrhus carcinoma of mammary gland. Note extensively fibrotic stroma.

The scirrhus type of canalicular carcinoma is of historical interest as it gave us the words "cancer" and "carcinoma." When it is untreated and allowed to progress, it converts the skin of the breast into a cuirass-like mass of stony tissue—the "*carcinome en cuirasse*" of the French writers. From this, ray-like processes extend over the skin, and the ancients, noting this, saw a fancied

resemblance to a crawfish. The Latin *cancer* and the Greek *karkinos* mean "crawfish," as does "Krebs" in German; other languages



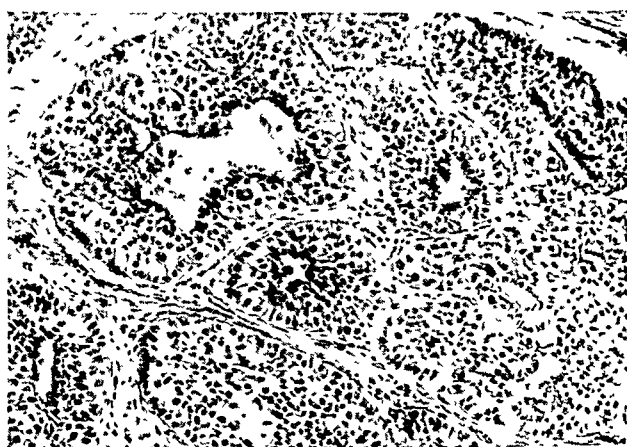
Cells of a scirrhus mammary carcinoma exhibiting distortion which follows irradiation with x-rays. They are about five times their usual size and exhibit vesiculation.



Field from "acute" carcinoma of breast. Here it bears little resemblance to epithelial tissue, its cells being notably discrete; elsewhere in the section (not shown here) they are grouped into typical epithelial complexes.

have followed suit. Another feature of the scirrhus carcinoma is the production of coarse, pitted skin like orange rind in its appearance; from this the clinicians get the French "peau d'orange" that describes the phenomenon.

Acute Type. This form is usually met with in connection with lactation; the breast becomes swollen, reddened, and hot and appears acutely inflamed. The tumor is large and poorly outlined, and on microscopic examination it is found to be so poorly differentiated and organized that its scattered cells (which fail to form cohesive complexes) resemble at first glance those of an inflammatory exudate. Closer inspection shows them to be polygonal epithelial cells, many of them in mitosis and all of them very



Typical field from lesion in "lobular carcinoma in situ." Cells are metaplastic and proliferative, but they do not stray from the canalicular complex. Patient from whom this was taken developed simple carcinoma two years after this tumor was removed.

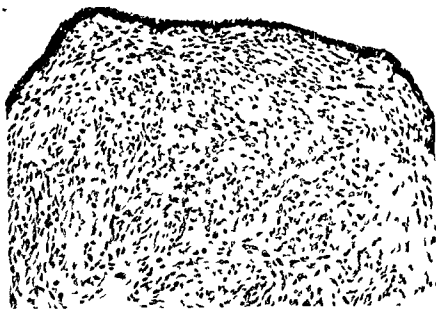
disparate in size and shape. This fortunately rare carcinoma is the most malignant of the mammary cancer types, and in its presence the prognosis is very bad. It metastasizes early to the axillae and into the thorax, from which it spreads to the viscera and bones.

"In Situ" Type. Lobular carcinoma in situ recently has been described and placed upon a firm histologic basis by Foote and Stewart. Grossly one notes a mammary gland that appears to be fibrocystic, but microscopically one finds areas of marked metaplasia of the canalicular lining cells which, although they may form small areas of local adenocarcinoma within the confines of the mammary lobule, do not tend

to leave it for the surrounding tissue. This gives rise to a lobulated tumor within the mammary gland which is the least malignant among mammary carcinomas and is often found in areas of fibrocystic disease of the Schimmelbusch variety. If these tumors are not removed, however, they may ultimately break out of the mammary lobules into the stroma at one point or another and produce

bulk, the epithelium usually remains essentially normal in type. Mitotic figures are easily found in the stroma. In spite of all this, the "bark" of this tumor is worse than its "bite," and when it is ablated it seldom recurs.

2. **Canalicular Fibroadenocarcinoma.** In this growth, which is very rare, the picture is reversed and the epithelium becomes defi-



Field from so called "cystosarcoma phyllodes." Note resemblance of picture to that of intracanalicular fibroadenoma on p. 406. It differs in that its stroma is sarcomatous and the papillae are much larger.

canalicular carcinoma of the scirrhus type with axillary metastasis.

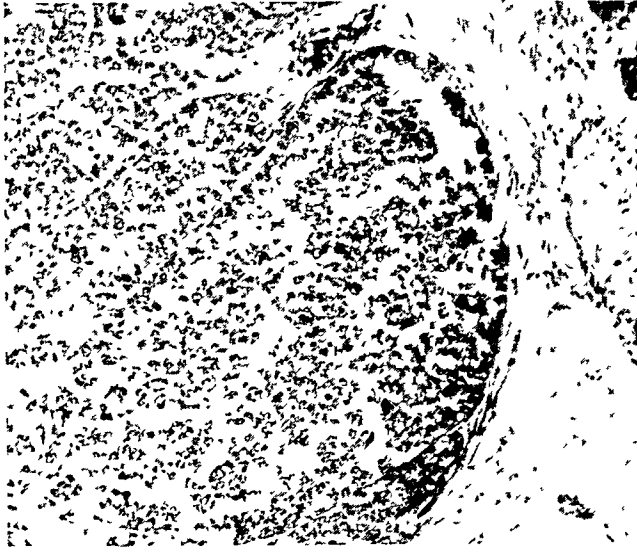
Mixed tissue Cancer. 1. **Intracanalicular Sarcoma.** This neoplasm has long gone under the imposing appellation of "sarcoma phyllodes cysticum"; it attains enormous proportions and causes a globular enlargement of the entire breast which may measure 30 cm. or more in diameter. The tumor is essentially a gigantically enlarged reproduction of the canalicular adenofibroma, with the difference that its stroma exhibits sarcomatous metaplasia, growing in the shape of giant papillae into the canaliculi and distending their epithelium unbelievably. Although the stroma is definitely sarcomatous, with poorly differentiated and often bizarre spindle cells constituting its

nitely carcinomatous, invades the stroma and infiltrates it widely. It is essentially a canalicular carcinoma developing within a canalicular fibroadenoma.

Acinar Tumors. Naturally, when there is uncertainty concerning the existence of acini in the normal breast, there is double uncertainty as to the possibility of an acinar carcinoma developing from these. Occasionally one may observe nonmalignant adenomas of a predominantly acinar architecture; they are grossly like the others described above, but microscopically they exhibit few canaliculi and many acini.

ACINAR CARCINOMA. There is little doubt that one very occasionally meets with a bulky, hard, and well circumscribed growth in the lower half of the breast, not far below

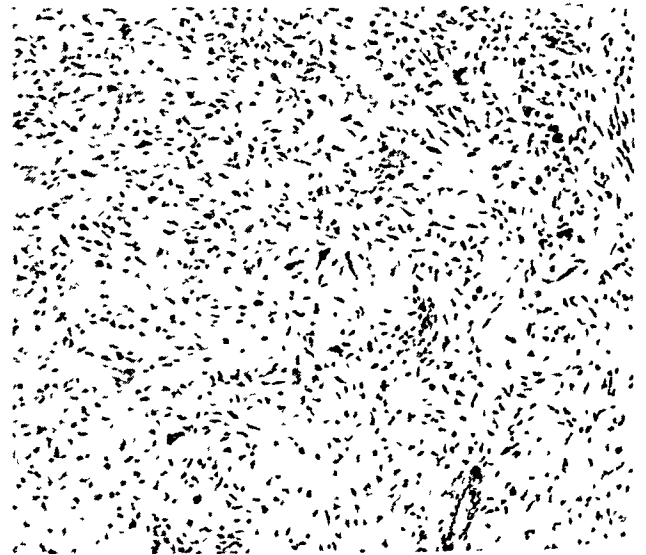
the nipple, which gives microscopic evidence of being acinar. The tumor is apt to be reddish and to exhibit areas of hemorrhage into its substance. It may be stone hard or comparatively soft and granular, and it may be fairly large when first seen by the surgeon (3 to 5 cm.). Under the microscope it is found to possess a rather simple histologic architecture of acini-comprising cells that vary from rather innocent-looking cu-



Field from so-called "acinar carcinoma." It differs from all other forms of mammary carcinoma in its vacuolated cells arranged in large alveolar groups

boidal elements to types that may become cylindrical and more malignant in their appearance. Sometimes the tumor may be composed of distinctly pleomorphic cells that are apt to produce neoplastic giant cells. Whether this tumor is really acinar in origin or not, it presents a distinct and readily recognized entity. It tends to metastasize rather late in its existence, and its sharp circumscription often tempts the surgeon to remove it locally and let it go at that. This is probably a mistake. On the other hand, the situation of these growths in the lower half of the breast makes the advisability of axillary dissection somewhat problematic, for if they are about to metastasize they will do so via the lymphatics that lead to the mediastinum, rather than to the axillae.

Reticulum-celled Sarcoma. Of the tumors that derive from the connective tissue of the breast, one of the rarer forms arises in the reticular tissue that forms a sheath about the canaliculi, ducts, and acini; this is chiefly composed of histiocytes. Neoplasms may originate there and form rather bulky, diffuse growths that metastasize to the axillary nodes, where they grow much more rapidly and malignantly than they did in the mammary tissue. Thus the metastases are wont to outstrip the primary tumor in size in a comparatively short time. Microscopically their appearance is typical of the reticulum-celled sarcoma. It may be difficult to decide whether they are primary in the axilla, metastasizing to the breast, or vice versa; careful observation of a patient who developed one while an inmate of our



Myxosarcoma from breast of young girl. Cells are relatively small, well differentiated, and stellate. Occasional neoplastic giant cells are visible.

hospital has convinced the writer that they actually originate in the mammary gland.

Mammary Tumors in Males. These are relatively rare; most of the male breasts removed for "tumor" prove to be the site of chronic fibrocystic disease or the hyperplasia that has been discussed under Gynecomastia. Occasionally specimens of adenofibroma are observed, but remarkably few have been received on our service in the

past decade. Malignant growths are even rarer, although they are occasionally noted, we have seen one scirrhus carcinoma in an elderly male during the above mentioned period. Reference to the literature would lead one to the belief that these tumors were observed with some frequency, Schu-

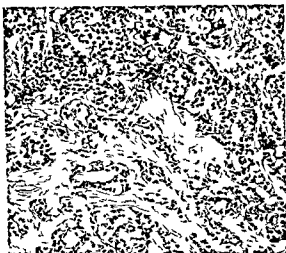
hardt (cited by Ewing) collected 269 tumors of the male breast, of which 244 were carcinomas and 3 sarcomas.

Tumors of Accessory Mammary Tissue. Accessory mammary tissue is heir to all these tumors, it is not at all uncommon to find both nonmalignant and malignant growths in axillary mammary tissue. Carcinoma of the apocrine axillary sweat glands must be distinguished from that of accessory mammary tissue. The largest intracanalicular fibro adenoma we have observed thus far in our hospital originated in an accessory gland in the axilla of a 14 year old girl.

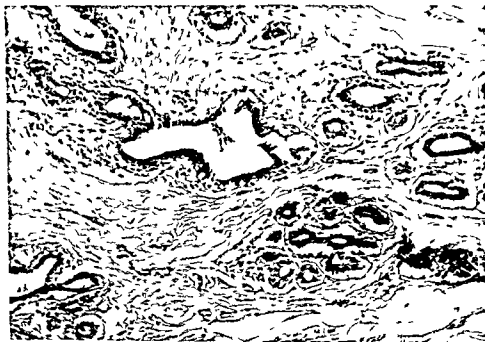
General Consideration of Cancer of the Breast

As almost half of the tumors of mammary origin that are sent to the laboratory prove to be cancer, it is necessary to stress the general pathology of this before leaving the subject.

Incidence. The rate of incidence of this malady increases progressively from youth to the early fifties, after which it falls slow-

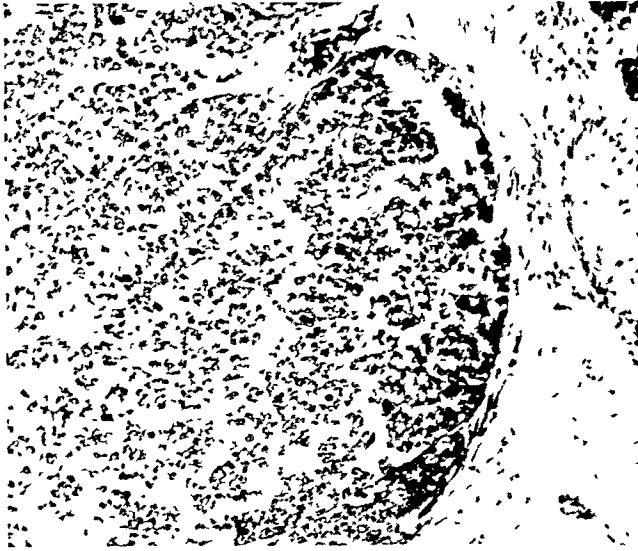


Adenocarcinoma of male breast. Although very common in women, this tumor is seldom seen in a general hospital in male patients.



Area of chronic fibrocystic disease occurring in aberrant mammary tissue removed from axilla. It differs in no way from typical mammary tissue in situ in breast.

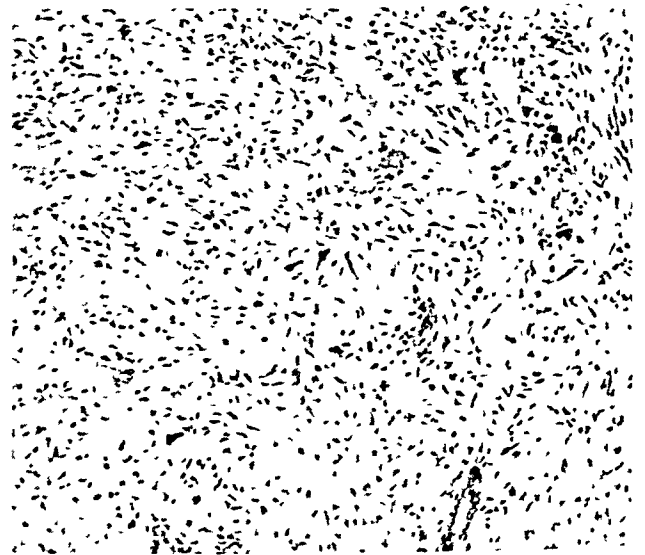
the nipple, which gives microscopic evidence of being acinar. The tumor is apt to be reddish and to exhibit areas of hemorrhage into its substance. It may be stone hard or comparatively soft and granular, and it may be fairly large when first seen by the surgeon (3 to 5 cm.). Under the microscope it is found to possess a rather simple histologic architecture of acini-comprising cells that vary from rather innocent-looking cu-



Field from so-called "acinar carcinoma." It differs from all other forms of mammary carcinoma in its vacuolated cells arranged in large alveolar groups.

boidal elements to types that may become cylindrical and more malignant in their appearance. Sometimes the tumor may be composed of distinctly pleomorphic cells that are apt to produce neoplastic giant cells. Whether this tumor is really acinar in origin or not, it presents a distinct and readily recognized entity. It tends to metastasize rather late in its existence, and its sharp circumscription often tempts the surgeon to remove it locally and let it go at that. This is probably a mistake. On the other hand, the situation of these growths in the lower half of the breast makes the advisability of axillary dissection somewhat problematic, for if they are about to metastasize they will do so via the lymphatics that lead to the mediastinum, rather than to the axillae.

Reticulum-celled Sarcoma. Of the tumors that derive from the connective tissue of the breast, one of the rarer forms arises in the reticular tissue that forms a sheath about the canaliculi, ducts, and acini; this is chiefly composed of histiocytes. Neoplasms may originate there and form rather bulky, diffuse growths that metastasize to the axillary nodes, where they grow much more rapidly and malignantly than they did in the mammary tissue. Thus the metastases are wont to outstrip the primary tumor in size in a comparatively short time. Microscopically their appearance is typical of the reticulum-celled sarcoma. It may be difficult to decide whether they are primary in the axilla, metastasizing to the breast, or vice versa; careful observation of a patient who developed one while an inmate of our



Myxosarcoma from breast of young girl. Cells are relatively small, well differentiated, and stellate. Occasional neoplastic giant cells are visible.

hospital has convinced the writer that they actually originate in the mammary gland.

Mammary Tumors in Males. These are relatively rare; most of the male breasts removed for "tumor" prove to be the site of chronic fibrocystic disease or the hyperplasia that has been discussed under Gynecomastia. Occasionally specimens of adenofibroma are observed, but remarkably few have been received on our service in the

- consideration of the blue domed cyst, *Arch Surg*, 3 445, 1921
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- Adenofibroma and fibro adenoma of female breast, *Surg, Gynec, and Obst*, 54 729, 1927
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ly until the age of 75 is reached. The curve is a very even one; its line rises steeply between the ages of 35 and 40, its peak represents the years from 50 to 55, after which it falls gently to the period from 75 to 80. (More details will be found in Ewing's discussion in his textbook.)

Etiologic Factors. Trauma formerly was believed to be very important, but its place as a significant factor has recently been usurped by endocrine disturbances. Ewing apparently considered stagnation of secretion to be important, citing Baggs's work on lactating rats, in which he tied off the ducts, caused retention and distention, and frequently produced carcinoma. Murray and Lacassagne both produced cancer in male animals by the administration of estrone, either by implanting ovaries or by giving the hormone by injection. With this in mind, castration has frequently been suggested as a curative measure, particularly in view of Huggins' work on the castration of males with prostatic carcinoma. The idea has not taken root, however, and surgery is still almost exclusively employed.

General Gross Features. Carcinoma in the breast is usually recognized by its stony hardness and fixation to the surrounding, underlying, and overlying dermal tissue. This applies chiefly to the more desmoplastic varieties, however; the acinar type is generally mistaken for an adenoma until it has been removed and examined. When one of the desmoplastic tumors is exposed it has a definitely cicatricial appearance, wholly unlike that of the well-encapsulated adenomas, adenofibromas, and "solid" or acinar tumors. (See view of scirrhous carcinoma in color plate.)

Ewing calls attention to the yellowish, chalky streaks of necrotic fat and desquamated epithelium that may be seen with the naked eye; they are, indeed, peculiar to carcinoma and very valuable in making a tentative gross diagnosis. Ewing feels that this is a much better guide to the presence of clinically malignant carcinoma than is the discovery under the microscope of an

area of frank carcinoma that fills only one 16-mm. field in an otherwise noncancerous gland. Carcinomas as small as this he was accustomed to ignore as indicative of clinically malignant growths.

Local Spread. Carcinoma spreads by the way of the periductal lymphatics; the skin is often invaded, and this phenomenon in the nipple causes the typical retraction that is almost pathognomonic; by contracting the connective tissue in the papillae of the skin it produces the "orange-skin" appearance already discussed (see p. 410). The pathologist always examines the pectoral muscles removed with a breast in radical mastectomy as a matter of routine, but invasion of the muscle is seldom demonstrable unless there is massive invasion in the immediate vicinity of the tumor.

Metastasis. There are three main routes of metastasis from mammary tumors: via the lymphatics to the axillary lymph nodes; to the lower cervical chains of nodes; and through the muscular lymphatics and intercostal channels to the mediastinum. The fact that most cancers are found in the upper and outer quadrant of the breast explains the frequent involvement of the axillary nodes on the same side; if the tumor lies mesial to the midclavicular line as this cuts the breast, a cross-metastasis to the contralateral axillary nodes may occur. Tumors in the lower half of the breast are wont to metastasize directly to the mediastinal lymph nodes, where they vegetate, sometimes for a few years, later metastasizing thence to other parts of the body, notably the bone, lungs, and brain. The mechanics of the metastasis of these tumors is admirably discussed on pages 581-583 of Ewing's *Neoplastic Diseases* (fourth edition).

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20

Nervous System

CONGENITAL DEFECTS
TRAUMA
INFLAMMATION
PARASITES
CEREBRAL TUMORS
CLASSIFICATION
TUMORS OF MENINGES

INFECTIOUS GRANULOMA OF SPINAL CORD
TUMORS OF SPINAL CORD
TUMORS OF PERIPHERAL NERVES
TUMORS OF NEURAL SHEATHS
TUMORS OF NEURAL TERMINALS
PAINFUL TUMORS ASSOCIATED WITH NERVOUS
SYSTEM

The surgical pathology of the nervous system is chiefly concerned with its neoplasms, which constitute one of the most

mas; occasionally he is asked to investigate biopsies of cerebral cortex or other nervous structures. On the whole, most of



Section from wall of a meningocele composed of meningeal tissue and sheets of neural tissue from spinal cord. This is the paler tissue in the photomicrograph.

frequent reasons for surgical intervention; inflammation and malformations play a distinctly subsidiary rôle. The surgical pathologist is called upon to examine pieces of excised cerebral scars and bits of meninges, as well as the walls of certain saccular structures like meningoceles and hemato-

his work has to do with the diagnosis of tumors removed from the central and peripheral nervous systems.

Congenital Defects. INCOMPLETE SPINA BIFIDA. In this anomaly there is failure of fusion of the posterior portion of the spinal canal, usually in the lumbar or lumbosa-

cral region, as a result of which a bulging sac may protrude under the skin, which may become very much thinned out. The wall of this sac may be composed of meninges with a few aberrant nerve fibers (meningocele), or of meninges and substance of the cord (myelomeningocele), or even of dilated cord alone (myelocele).

SPINA BIFIDA OCCULTA Here there is no bulging sac, although there is a defect in the fusion of the spinal processes. The overlying skin may show pigmentation and a "satyr's tail" of long hairs, or a variety of tumors—usually lipomas, sometimes neural tumors—may develop in the region.

TUBEROSCLEROSIS Biopsies of cerebral tissue taken at an exploratory operation may show the lesions of this generalized disease, which includes retarded mental development, retinal tumors, sebaceous hyperplasia of the skin, and other less important lesions and signs in its pathologic picture. The disease develops in early life and may be hereditary. The cerebral lesions consist of globular structures a centimeter or so in diameter that are usually found in the cortex and distort its architecture. Histologically these are composed of neuroglial fibers and somewhat atypical astrocytes that readily mislead the pathologist into thinking that the nodules are small astrocytomas. The lesions may become somewhat cystic. The disorder is believed to be due to faulty development of the brain, involving chiefly the cortex, but also noted in the white matter and in the walls of the ventricles.

HYDROCEPHALUS The surgical operations involved in this condition are chiefly calculated to drain the superabundant cerebrospinal fluid from the distended ventricles or to prevent its secretion by removal of much of the choroid plexus. Therefore there is little material to work with except in the latter instance, when it is largely destroyed by being removed with a fulgurating current. Even when material is available there is usually little to be learned from the examination of the cho-

roid, which may exhibit a little hyperemia or appear to be somewhat hyperplastic. The condition usually occurs in infancy; it may be congenital or acquired and it leads to the characteristic enlargement not only of the brain but of the skull as well. When it is seen in adults as an acquired lesion it cannot expand the skull and is not so readily diagnosed.

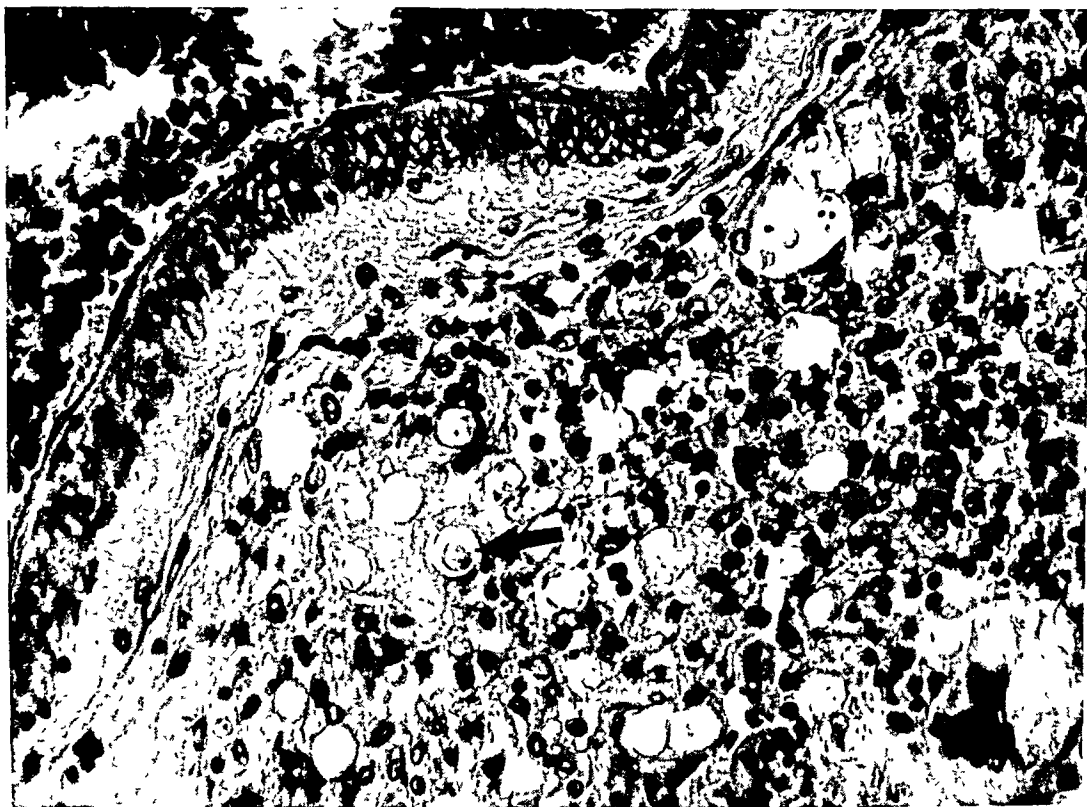
Trauma The most common condition requiring surgical intervention to relieve intracranial pressure is the subdural hemorrhage which may follow trauma or may occasionally occur spontaneously in the case of local inflammations resulting from a variety of causes such as infectious diseases, hemorrhagic affections, and the like. Usually situated in the parietofrontal area, the subdural hemorrhage produces lens-shaped masses of extravasated blood that undergoes degeneration, becomes muddy brown, and is surrounded in a very short time by enveloping membranes that may simulate those of the brain in their histologic appearance. They do not show any arachnoid villi, however, and they are composed of very loose connective tissue. Just beneath this highly vascularized membrane the clot becomes organized, with the new tissue growing centripetally and gradually replacing the clot. Secondary hemorrhage from the newly formed membrane may be a troublesome or even fatal complication. Subarachnoid hemorrhages may also occur, particularly in connection with small aneurysms.

Inflammation MENINGITIS The acute inflammations do not concern us here but there are forms of chronic meningitis that may lead to adhesions between cortex and dura which are often dissected out in an attempt to alleviate a form of epilepsy which may be attributable to them. In chronic leptomeningitis the membrane is thickened and milky, at the same time becoming more opaque than normal. This leads to the formation of a patch of scar-like thickening that constitutes an "adhesion." This condition may be ascribed to various causes, such

as alcoholism, lead poisoning, and certain infectious agents. Syphilitic meningitis is not at all uncommon, and an examination of the meninges in this disease will reveal a lymphocytic exudate and angiitic lesions in the vessels.

ENCEPHALITIS. Cerebral abscess is the usual outcome of an intense, localized, and

singly but may be multiple. Its usual site is the cerebellar or cerebral cortex. It presents as a dirty, greenish-yellow mass that is well circumscribed and obviously necrotic at its center and firmer toward the periphery, but not liquefied nor surrounded by any obvious zone of hyperemia. It is more usual among children than adults.



Granuloma at edge of a pial vessel in torular meningitis, which is a rare condition. Near center an arrow points to one of the torulae in a vacuole; many others are visible in vacuoles in giant cells. Note large giant cell at lower right.

acute encephalitis; this is frequently surgically "unroofed." The pathologic picture is one of banal inflammation and necrosis; therefore it needs no description. The association of the lesion with traumatic infection, sinus thrombosis following middle-ear infection, acute infections, and metastatic abscesses from the lungs or from infected bronchiectases should also be mentioned.

INFECTIOUS GRANULOMA. *Tuberculosis.* Such tuberculous infections of the brain as miliary tuberculosis do not concern us, but the so-called "tuberculoma" or solitary tubercle does, as it may be mistaken for a tumor and operated upon. It is a large conglomerate tubercle that usually develops

Syphilis. A solitary gumma, like the solitary tubercle, may be mistaken for a tumor; it occurs in later life, lies rather superficial in the cortex, is irregular in outline, and is surrounded by a zone of fibrous capsule. Its origin is in a meningeal vessel or in one of the submeningeal plexus of the cortex.

Parasites. *Endameba histolytica* has been reported as causing cerebral abscess, and the lung fluke *Paragonimus ringeri* may be found in the brain, although no surgical intervention will avail.

The commonest parasite is the *Cysticercus* of one or another tapeworm, although the much improved modern methods of in-

specting meat have cut down the incidence of such infestations conspicuously. The *Cysticercus* is the embryo of the tapeworm and may become encysted almost anywhere in the brain, although usually it is found in the cortex and in the walls of the ventricles. Here it may simulate a tumor and be removed by operation. If the infestation



Cysticercus of *Taenia saginata* embedded in parietal lobe of brain. Note capitellum with two "suckers" visible. Absence of hooklets distinguishes this from *cysticercus* of *Taenia soleum*.

take the form of multiple cysts the outlook for successful surgery is naturally poor.

The embryos of *Taenia soleum* and *T. saginata* are most often found, as they represent common parasites of the hog and of cattle. Another taenia, *T. echinococcus*, may infest the brain, although it favors other sites such as the liver, lungs, and spleen. The broad tapeworm, or "fish tapeworm," *Diphyllobothrium latum*, is not at all dangerous in this respect, although it is the most formidable of the group, as its larvae live only in fish and would die in a warm-blooded host.

Cysticerci are composed of the invaginated head of the embryo, with its rostellum (surrounded by hooklets or suckers) turned inside out and projecting into a cyst like segment or early proglottid which is known as "the bladder." This retraction and inver-

sion of the head leads to a picture in microscopic sections that is complicated and puzzling to reconstruct. Surrounding the *Cysticercus* there is a wall of condensed cerebral tissue with an admixture of collagenous fibers from the walls of vessels in the vicinity, the whole making up a small globoid mass about a centimeter or so in diameter. This is readily enucleated from the cerebral tissue.

Microscopic examination will show hooklets on the rostellum of *T. soleum* and none upon that of *T. saginata*. A history of having eaten undercooked pork should be elicited in the case of the former, of indulging in raw or smoked beef in that of the latter.

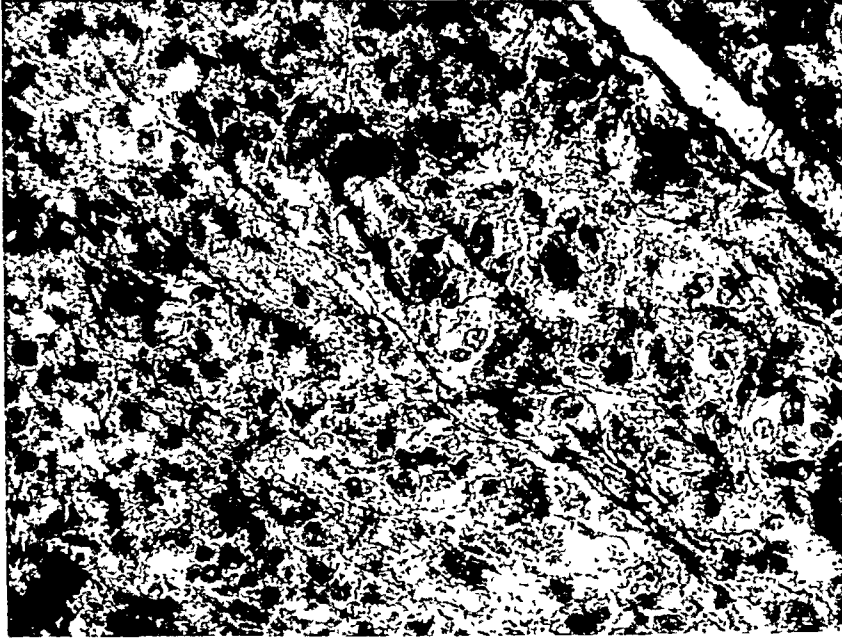
BRAIN

Tumors. Time was when any tumor of the brain was a "glioma" and one of the cord or peripheral nerves a "neuroma," but unfortunately the matter has proved to be much less simple than that. The classification, and with it the understanding of gliomas, was a most haphazard affair until Bailey and Cushing combined their neuropathologic and clinical talents to devise a scheme for classifying such tumors upon an embryologic or histogenetic basis. This was in 1926, only a couple of decades ago, since then great strides have been made in our understanding of cerebral tumors and of what is to be expected as a result of their presence. This is a good example of the benefit accruing from a systematic classification. Arranging the genealogic schemata of development reproduced in the accompanying charts, they proceeded to hang each tumor upon the cell from which it was presumably derived ("presumably" because, as Ewing was wont to insist, the neoplastic cells are not identical in their appearance with that of their putative embryologic forebears).

In the first schematic diagram the "medulloblast" is a type introduced as a transitional stage and liaison member belonging between the spongioblasts and the neuroblasts, it is a hypothetical cell and not an

embryologic entity. The microglia at the bottom of the diagram was queried in Bailey and Cushing's original chart; it proves to be none other than the ubiquitous and versatile macrophage which has access to the brain from its vascular system. It is therefore an alien cell and does not strictly belong in the company of the neural and neuroglial elements, although it is found there sufficiently disguised to have fooled

the schemae; it should be realized that brain tumors are often infiltrative affairs that fail to form compact, homogeneous masses of similar cells sharply set off from the surrounding neural tissue. Instead, they include many of the elements of that tissue, and for this reason an astrocytoma may show many oligodendroglia and neurons included in a loose complex of astrocytes. This will complicate the picture to



Cajal-Nonidez impregnation of a glioblastoma multiforme to demonstrate infiltration of tumor among neurofibrillae. The fine, wavy black lines are fibrillae.

neuropathologists and pathologists for many years. It used to pass under the name of "compound granular corpuscle." Silver impregnation revealed that it possessed very complicated "mossy" processes; the same method revealed entirely similar cells in exudates in other parts of the body.

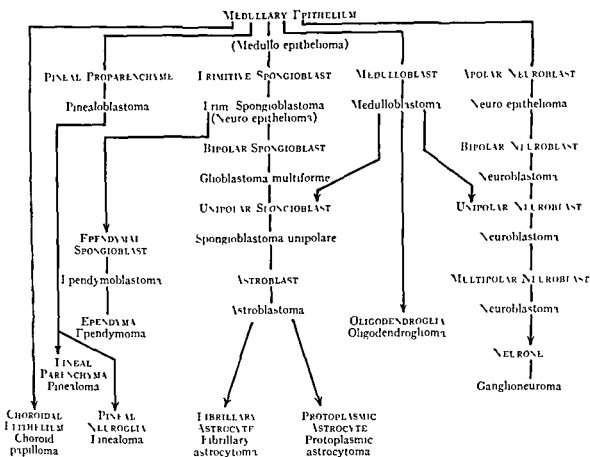
These schemae and the one that will follow shortly are taken from the book of Bailey and Cushing with slight modification; they are based upon embryologic and experimental evidence and constitute an excellent scaffold from which to erect a systematic description of the various forms of neural tumors. They will be utilized to this end, some differences of opinion being noted as we proceed.

Bailey and Cushing recognize fourteen categories based upon the type-cell listed in

such an extent that one may wonder whether one is dealing with an astrocytoma or merely a focus of astrocytic proliferation and gliosis. In such cases it is well to determine that cell which represents the majority in the tumor and consider it the type-cell. It should also be understood that gross descriptions of cerebral tumors are exceedingly difficult to express, as many of them look like slightly altered areas in the cerebral tissue; glioblastomas are a good example, as in the cortex are found yellowish, distorted foci which might often represent almost anything.

MEDULLO-EPITHELIOMA. There were only two of these in the series of 254 cerebral tumors examined by Bailey and Cushing. Medullo-epithelioma or medullary epithelioma is a very rare tumor that occurs in

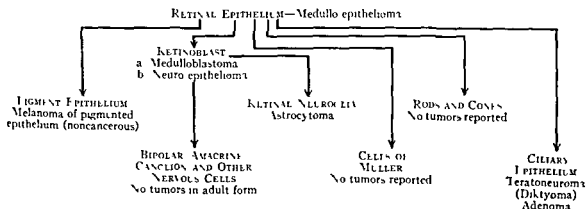
CHART I



(MICROGLIA)

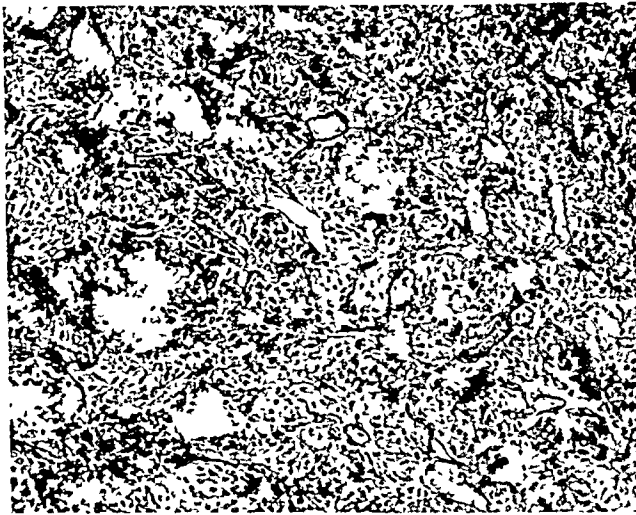
Retothelial tumors

CHART II



the floor of the midbrain and third ventricle. It is very inaccessible to operation and it grows rapidly. It shows no particular predilection for old or young subjects. Microscopically it is composed of definitely epithelial cells that form no fibrillary stroma, have abundant cytoplasm and oval nuclei, and may become columnar when they radiate from vascular sinuses. Otherwise they are fusiform. They show numerous mitotic figures and have an architecture that is one of multiple circles about vessels.

MEDULLOBLASTOMA. Bailey attributes this tumor to a multipotential cell which he has



Unusually glandular and primitive medulloblastoma of pituitary region. There are no pseudorosettes in this form of the tumor.

named the "medulloblast" or "indifferent cell of Schaper." Other authorities incline to the idea that these are neuroblastic, arising from the granular layer of the cerebellum, where they are most frequently found. Bailey's intention in calling these "medulloblasts" is to connote that they are found in tumors of the medulla which show a mixture of neurones and neuroglial cells in immature forms; reference to the schema will illustrate his belief that they may shift into three lines of descent. One of these is spongioblastic, another oligodendroglial, and the third neuroblastic.

Medulloblastomas occur chiefly in the midline of the cerebellum in children and

have an average age incidence of ten years. In older subjects they arise in the roof of the fourth ventricle and occasion hydrocephalus by compressing the outlets of the ventricles. They have a tendency to invade the leptomeninges and spread along the arachnoid spaces, which is a unique feature in cerebral tumors (excepting meningiomas).

Grossly they are soft and pinkish in color. Microscopically they are composed of cells similar to those of the preceding tumor, but these tend to be arranged into "false" rather than into "true" rosettes. True rosettes are arranged about an empty lumen; the false variety are less definitely glandular in their appearance, and the cells that compose them are apt to have fibrillary processes that extend into the lumen of the rosette, entangling themselves with those of neighboring cells and filling the space with a sort of loose felting. These do not stain in a manner that proves them to be neuroglial fibers, neurofibrillae, or connective tissue; they would indicate that they are protoplasmic and filamentous processes from the cytoplasm of the medulloblasts. They may exhibit long rows of clumped nuclei.

As both neuroblasts and spongioblasts may be demonstrated in these tumors, Bailey introduced his bipotential medulloblast to explain the phenomenon. When the growth spreads into the cord it may secrete itself out along that structure and become so much like a lymphosarcoma in its appearance that it may be mistaken for one. Similar tumors are found in the retina, where they used to be called "retinal gliomas," but they are now known as "retinal blastomas" which have two subtypes: the medulloblastomas and neuro-epitheliomas. Medulloblastomas occur not only in the retina, but in the peripheral sympathetic nervous system, where they are known as "sympathoblastomas"; these will be discussed later.

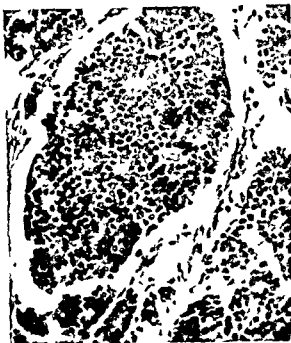
(Chart II is included as an aid in correlating cerebral and retinal tumors. It will not figure otherwise in this discussion.)

PINEALOMA AND PINEALOBLASTOMA These are neurogenous, but for the sake of conformity with usage they are discussed in connection with the pathology of the ductless glands, or organs of internal secretion.

EPENDYMOMA AND EPENDYMOBLASTOMA Growths arising in the ependymal spongioblastic tissue are known as "ependymoblastomas," while those that originate in the better differentiated and more mature ependyma are called "ependymomas." The ependymoblastoma is possibly no more malignant than the ependymoma, it may exist for a long time in a latent state usually in the midcerebellar region. It is firm, pale, and nodular, not pinkish and soft like a medulloblastoma. It tends to extend downward into the cistern. The average age in incidence is 13, this is decidedly a tumor of childhood. The ependymoma has a similar gross appearance, but does not manifest its presence until the average age of 25. This may merely be a matter of slower growth.

Microscopically the two tumors differ in academic respects, but this difference is elusive in practice and it is difficult to diagnose the two forms definitely. In the ependymoblastoma the microscopic structure is one of cells packed between small vessels from which they are separated by clear zones which, when sections are properly stained, are found to contain the polar processes of the cells. Mitotic figures are very rarely noted. One may demonstrate groups of small spherical bodies in the cytoplasm of the cells. They are known as "blepharoplasts" and represent the motor apparatus of cilia that are lacking; thus, instead of lining up under the cilia they merely form globular groups near the end of the cell that would be ciliated had it developed that far. While not pathognomonic of ependymal cells, blepharoplasts are rarely seen in other cells, except in such primitive tumors as the neuro epithelioma. The ependymoma differs from its less mature relative by not producing polar cells, being characterized instead by more simple, polygonal elements

NEURO EPITHELIOMA Bailey and Cushing collected no example of this tumor. It is decidedly rare in the brain. Tumors that might fall into this category have been reported in the aqueduct and along the spinal cord. They are also found as one of the subtypes of retinoblastoma in the eye. Similar tu-



Field from malignant retinoblastoma that had metastasized to base of aorta. Note well formed rosettes and the mitotic figure in upper left hand margin of main group of cells (Courtesy of Dr. Flimm, Cincinnati General Hospital).

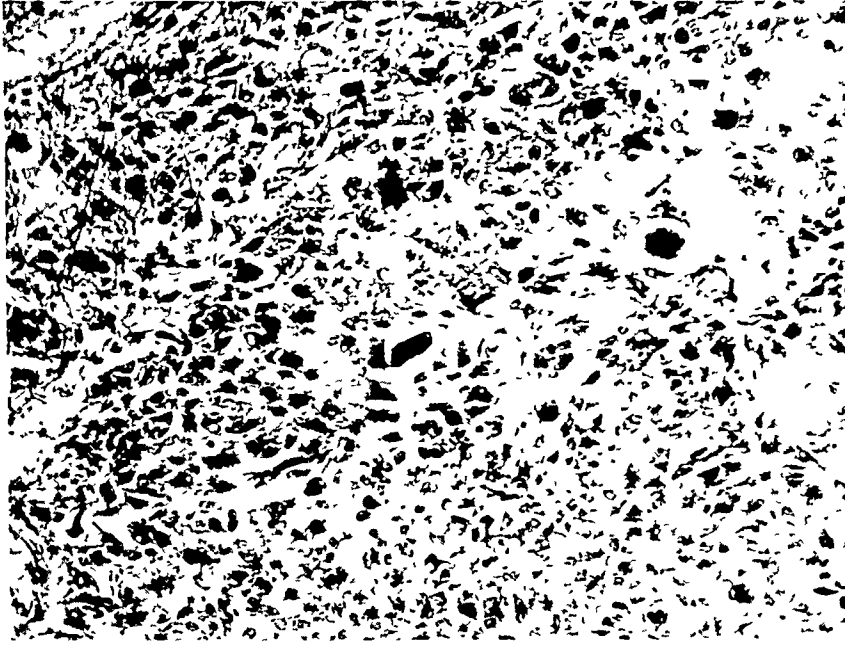
mors, as will be seen later, are described in the course of peripheral nerves. Bailey and Cushing believed that all these represent primitive spongioblasts, but retained the name "neuro epithelioma" for convenience and because it is well rooted in the literature. Microscopically the tumor is found to be composed of primitive spongioblasts that arrange themselves into gland like true rosettes with the rather columnar cells radiating from an empty lumen. They may exhibit cilia and blepharoplasts. In the retinal form these cells have been interpreted as immature rods and cones, but this is disputed. If they do represent rods and cones,

which are functional neural elements, this fact would throw at least the retinal form of this tumor into the category of "neuroblastoma," removing it from the true "gliomas."

SPONGIOBLASTOMA. There are, as one might suppose from the schema, several varieties of spongioblastoma representing different stages in the development of the astrocyte.

is unique among the cerebral tumors in invading "foreign" tissue. Out of the 77 examples mentioned, only five survived over three years.

The spongioblastoma's extensive invasiveness of the cerebrum and its tendency to recur make its complete eradication difficult or impossible and render its prognosis grave. Irradiation has been extensively experi-



Silver impregnation of glioblastoma multiforme to demonstrate its truly multiform appearance and the thickened neuroglial fibers.

The most frequently encountered type is the glioblastoma multiforme, which is supposed to develop from bipolar spongioblasts but, owing to degenerative and reparative processes, takes on a multiplicity of cellular morphology that would be bewildering were one to catalogue all its varieties. This neoplasm forms 77 of the 254 tumors classified by Bailey and Cushing. It tends to infiltrate widely and to recur repeatedly. It is a tumor of middle life, with an average age incidence of 41, usually arising in one of the cerebral hemispheres; only 2 of the 77 just mentioned were in the cerebellar hemispheres. Although, unlike the medulloblastoma, it does not invade the leptomeninges, it has been known to penetrate decompression wounds and invade the muscular and other tissue, extending down into the neck. This

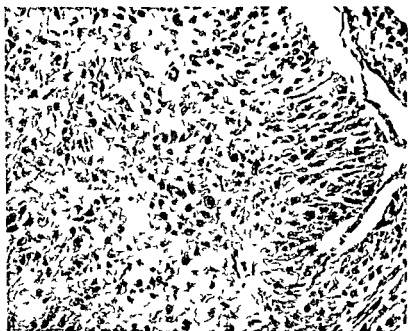
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does not metastasize, and this absence of metastasis is true in the case of the spongioblastic groups throughout

SPONGIOBLASTOMA UNIPOLARE Unipolar spongioblastomas may be found in various situations in the brain, with a predilection for the cerebellum. They are tumors of early life and tend to undergo extensive cystic degeneration, so that they may be known

as "cerebellar cysts." The average age in incidence is 15, although they may be found in adults of 40 or so. Running a slow and nonmalignant course, their situation in the midbrain and cerebellum near vital neural pathways makes their extirpation hazardous and renders operative prognosis much graver than their absolute composition and appearance would warrant. They are composed of parallel or less orderly lines of unipolar spongioblasts that show a tendency to undergo slow degeneration and to form the cysts that characterize the tumor grossly. There is a distinct similarity in their appearance to that of the "acoustic neuroma" of the eighth nerve, this similarity is so great that one frequently ponders the possibility of fusion of the two types as the nerve emerges from the midbrain. Mitotic figures are not usually found.

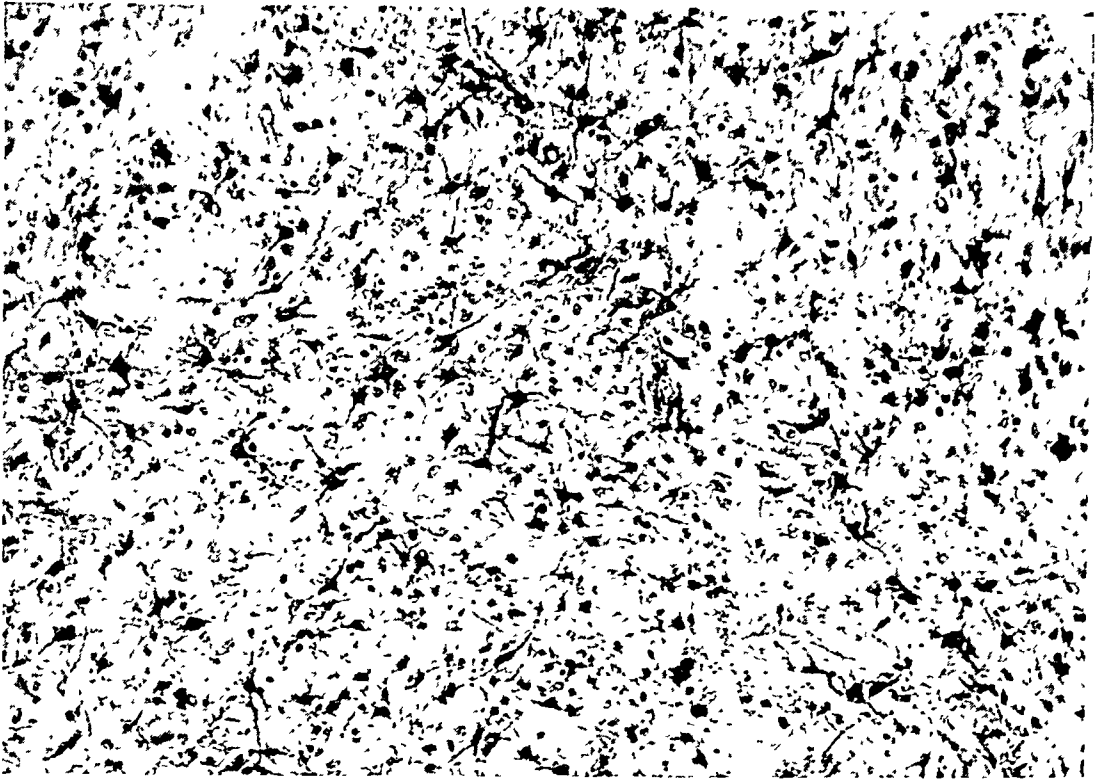
ASTROBLASTOMA The astroblastoma is a tumor of later life, with an average age incidence of 40 to 50. It usually occupies part of a cerebral hemisphere which it infiltrates so extensively that it is difficult to outline and hence to remove. It shows no tendency



Astroblastoma composed of large multipolar cells, some with fibrillary, others with protoplasmic cytoplasm. This variability distinguishes the tumor from the astrocytomas.

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of fusion of the two types as the nerve emerges from the midbrain. Mitotic figures are not usually found. As it has a very indefinite gross appearance, lying just beneath the cortex, it is not strange to find that the microscopic picture is in the nature of a hodgepodge of neoplastic and normal cells all intermingled. One sometimes despairs of making a definite diagnosis of neoplasm, so much does the picture resemble some sort of infiltrating neurogliosis. The type cell is a plump, triangular astroblast that is loosely associated with others like it and often exhibits a stout vascular process or "foot" attached to a neighboring capillary wall. Its growth is slow, and mitotic figures are not seen. There may be some confusion between this and the neurocytoma or ganglioneuroma that arises in sim-



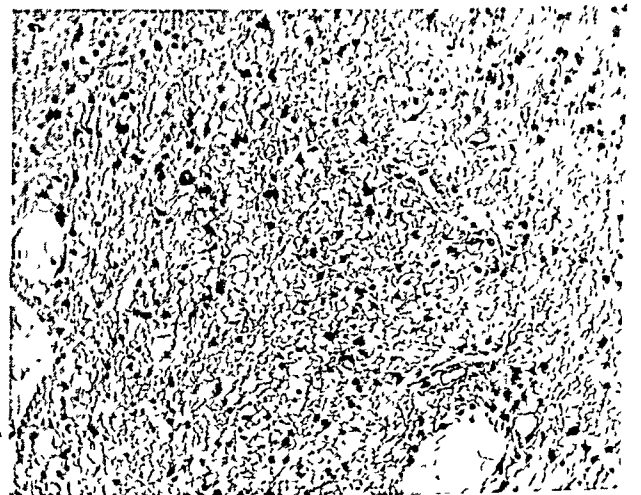
Fibrillary astrocytoma. Note slender multipolar astrocytes and generous admixture of cells that were resident in invaded tissue.

ilar situations and is composed of large triangular cells. These, however, exhibit Nissl bodies and may show axones in silver impregnations; they lack vascular processes, which are peculiar to the spongioblastic family.

ASTROCYTOMA. As there are protoplasmic and fibrillary astrocytes, one might expect to find tumors corresponding with these two cellular types, and Bailey and Cushing recognized these in their book. In young people both tumors are situated in the cerebellum, in an older age group in the cerebrum. For the protoplasmic astrocytoma the average age incidence is 29; this may be broken down to an average of 13 for cerebellar tumors and of 35 for the cerebrally located examples. The fibrillary variety shows a similar over-all average of 23, and almost all the examples were in the cerebellum in patients ranging from 3 to 48 years of age. Both varieties tend to undergo cystic degeneration; the protoplasmic astrocytoma may be so soft and gelatinous that most of it may be removed with the suction apparatus. Fibrillary astrocytomas carry a less favorable prognosis when they occur in

the cerebrum, but the prognosis in all forms of this tumor is much better than it is in most of the tumors we have been discussing, and it is stated that in 40 per cent of the lesions there is nothing that need be greatly feared.

Microscopically the protoplasmic variety is composed of protoplasmic astrocytes in



Well-differentiated fibrillary astrocytoma impregnated with silver. Tissue resembles normal neuroglia, but lacks functional neurocytes of cerebral tissue. The small cysts are common in non-malignant cerebral tumors.

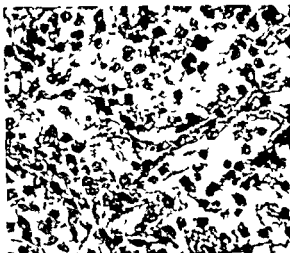
loose arrangement that is often crisscrossed by surviving neurofibrils that traverse it. The fibrillary astrocytoma is much firmer and is composed of fibrillary astrocytes embedded in a firm and fibrous matrix of neuroglial fibers. It is not very vascular. Calcification may be noted and may be of assistance in the roentgenologic diagnosis.

The microscopic types just noted are found, unfortunately, only in very typical tumors, most of the astrocytomas exhibit a mixture of the two forms of astrocytes, just as the normal cerebral tissue should. For this reason Bailey, in a later article, included both groups in the simple category of "astrocytoma" and stated that "these well known lesions are composed of almost completely developed neuroglial cells, astrocytes, either fibrillary or protoplasmic, usually both."

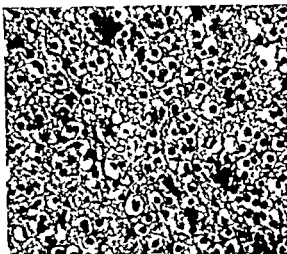
INFUNDIBULOMA Globus has recently described a rare tumor that develops in the interpeduncular space near the infundibulum. It is usually spheroidal, 1 to 2 cm in diameter, and it spreads into the stalk of the hypophysis which it invades to the posterior lobe. There are peculiar vessels arising near the surface of the fetal infundibulum and running upward within its substance. They branch laterally at right angles and are surrounded by a compact layer of neuroglial fibers that form a spiral sheath. These vessels gradually diminish in number as adult life is reached, but may reappear in later life. The tumors which arise here are characterized by the presence of these peculiar vessels with branches like those of trees *en espalier*, surrounded in this instance not by neuroglial fibers, but by radiating astrocytes with vascular processes or feet. The bulk of the tumor is composed of long polar cells not unlike spongioblasts and would apparently fall into that category.

OLIGODENDROGLIOMA Bailey and Cushing hesitated to classify this tumor definitely and marked it with a (?) for a while, Bailey's later article still queried the name, but time has justified it amply, and the question mark no longer mars the effect of

its rotund syllables. The tumor was at first considered to occur anywhere in the brain, but it has been found to prefer the



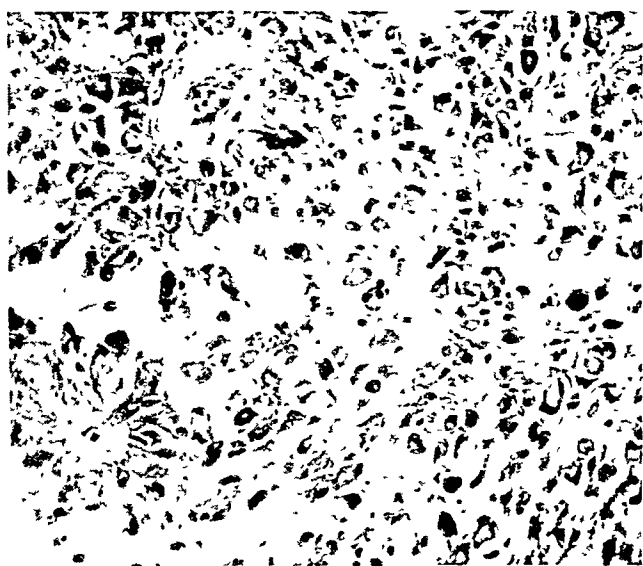
Oligodendroglioma impregnated with silver. Paucity of cellular processes gives the type cell its name "oligodendroglia cyte."



Silver impregnation of degenerative form of oligodendroglioma, the cells of which occupy lacunae apparently formed by accumulation of fluid about them.

frontal lobes near the midline. It has been proved to be not at all uncommon now that Bailey and Cushing have pointed out its salient features. It is a pinkish growth that may attain large size, although it grows slowly. It probably starts early in life, not giving symptoms until young adulthood is

reached, and usually it is well encapsulated. Microscopically it is found to be composed of small spherical cells about the size of lymphocytes; these, with special impregnation, exhibit a few short processes (oligodendria) that are apt to terminate in rounded knobs. Under ordinary stains, however, they are seen as spherical cells with a vague halo of cytoplasm and spherical, dark nuclei.



Section from true neuroblastoma of frontal area of brain. It has a superficial resemblance to glioblastoma multiforme, for which it is readily mistaken, but can be differentiated therefrom by appropriate impregnation with silver. Its type cells are essentially ganglionic cells.

They may appear to occupy vesicular spaces in the cerebral tissue in the case of some of the tumors in which degeneration has been going on. Mitotic figures are not seen in these tumors.

NEUROBLASTOMA. Use of this name for the sympathoblastomas has produced confusion. It should be used for growths derived from cerebral neuroblasts and discarded in connection with the sympathoblastomas. On gross examination neuroblastomas cannot be distinguished from gliomas; they usually are found in the cerebral hemispheres in the frontal area. They are sharply demarcated and run a nonmalignant course, although malignant varieties occur in the sym-

thetic ganglioneuromas. In order to distinguish them with certainty from any bulky tumor of the hemispheres they should be fixed in chloral hydrate; this will permit of a Ramon y Cajal silver impregnation that will reveal neurofibrillae in connection with the neoplastic cells. Nissl stains with cresyl violet will bring out the tigroid bodies in the cells, which will also identify them as neural and not neuroglial. The tumors run the gamut from poorly differentiated polar neuroblastomas to highly organized ganglioneuromas with unmistakable ganglion cells.

To mistake a neuroblastoma for a glioblastoma would be a serious mistake on account of the innocence of the one and the malignancy of the other. Neuroblastomas are considered rare, but careful investigation of tumors of the cerebral hemispheres with appropriate methods may show that they are not quite so unusual as is believed.

CHOROID PAPILLOMA. This arises in the covering cells of the choroid plexus and is situated in or near that plexus. It is composed of bright red papillary structures that on microscopic examination are found to have vascular cores and a covering of more or less cuboidal cells which may be ciliated.

OTHER TUMORS IN THE BRAIN. The brain is a favorable site for metastasis, so that one should always be on one's guard against failing to recognize a growth as entirely foreign to that organ. A variety of carcinomas, leukemic tumors, sarcomas and the like may metastasize to this organ. Carcinoma of the breast, bronchi, prostate, and kidney are frequent offenders. Aside from the cerebral tissue, there is only the connective tissue about the vessels and the endothelium of these from which tumors might arise primarily. Angiomas, angiosarcomas, and tumors originating in the perivascular histiocytes may be observed, the last being essentially a "microglioma," although never called by that name. Tumors and cysts of Rathke's pouch may be found at the base of the brain. Cartilaginous or bony tumors

may penetrate from the skull or the vertebrae or may arise from misplaced bits of these

MENINGES

Tumors MENINGIOMA During those years when one spoke of "pleural endothelioma" the meningiomas were called "dural endotheliomas", next they were

Eisenhardt published an excellent and inclusive monograph on the subject, classifying the meningiomas into a goodly number of categories

Meningiomas are slowly growing tumors that develop in the leptomeninges at those sites where paccchionian bodies are found along the sagittal suture and the attach

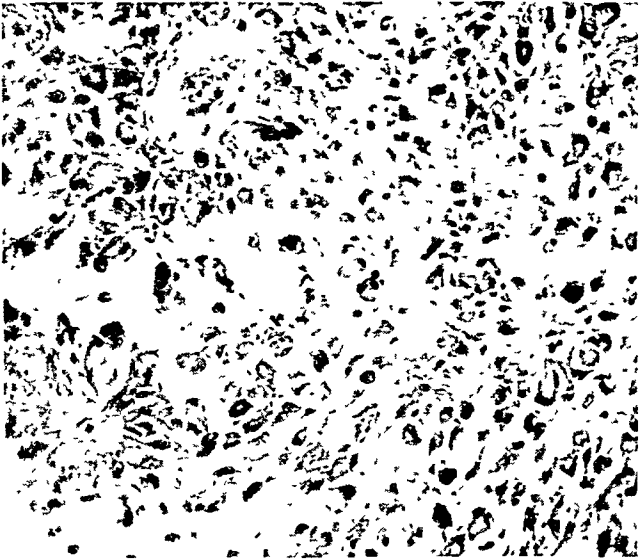


Silver impregnation to demonstrate reticulum of meningioma of falx cerebri
Note its abundance and its stellate and whorled arrangement

known as "arachnoid fibroblastomas," which came a little closer to describing them and is a term still applied by some authorities. Now they are largely known as "meningiomas" and their type cells are recognized as meningocytes derived from the ganglionic crest and therefore of ectodermal origin. There is still much dispute over the question as to whether these cells are not really mesenchymal. The experimental work of Harvey and Burr, Raven and others seems to be fairly conclusive as to their ectodermal origin. They were first recognized as differing from ordinary mesenchymal tissue by Oberling, whose theories were received with undue scepticism until this experimental work indicated their validity. Cushing and

ments of the tentorium, for example. They are yellowish brown, flattened, and rather lenticular, their consistence is very firm, and they have a fibrous admixture that varies with the microscopic type of the growth. They are not limited to the cerebral meninges, being found also in the spinal cord, where they often arise in several places at once, appearing to be multicentric in origin. They occasion symptoms of intracranial pressure and may invade bone or provoke its massive overgrowth, so that there will be a domed thickening of the skull in the area overlying the tumor that almost exactly corresponds with it in size. Meningiomas appear to have osteoblastic capacity in their own right, sometimes forming car

reached, and usually it is well encapsulated. Microscopically it is found to be composed of small spherical cells about the size of lymphocytes; these, with special impregnation, exhibit a few short processes (oligodendria) that are apt to terminate in rounded knobs. Under ordinary stains, however, they are seen as spherical cells with a vague halo of cytoplasm and spherical, dark nuclei.



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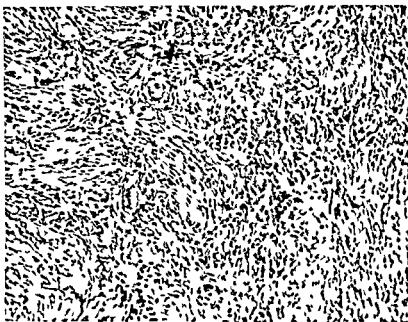
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Fibrous type of meningioma exhibiting less tendency for formation of whorls, the cells being arranged in bands and bundles

ningeal hemangiomas, etc., rather than as forms of meningioma

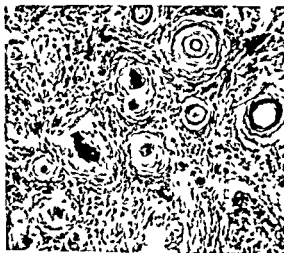
Meningocytic or Arachnoid Villous Type

This is a common form of the tumor in which meningocytes form whorled groups of cells arranged about a center—usually a small vessel or a knot of collagenous tissue. Their fibrous stroma is scanty. The cells are fusiform or somewhat flattened and squamous and have a rather copious cytoplasm, so that they resemble epithelium or endothelium strongly.

Mixed Type In this there may be greatly increased amounts of fibrous tissue, analogous to that of a scirrhous carcinoma but not as dense, which may overshadow the presence of rather inconspicuous groups or cords of meningocytes that are too compressed by the fibrous tissue to form whorls. This type is very apt to possess large numbers of calcific granules that are concentrically laminated and are known as "psammoma bodies." These are normally present in pacchionian bodies in elderly subjects and in the pineal gland (See color plate.)

Pigmented Type This is mentioned with due reserve for it has been described only by Ray and the writer, and more cases should be collected and studied. It appears

to be rare, as we have had but two examples in the hospital in the course of twelve years. One finds deeply pigmented tumors in the



Psammomatous type of meningioma containing target like psammoma bodies which are partially or entirely calcified

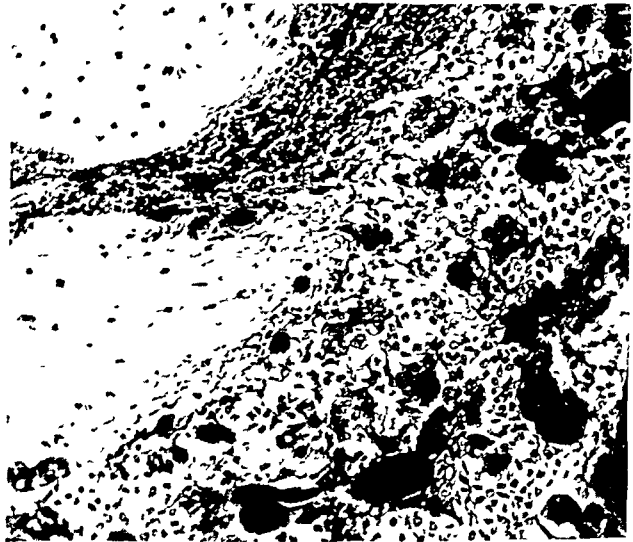
meninges of the brain, more particularly of the spinal cord, that would be identical in structure and appearance with the meningioma were their pigment removed. They do not show the architecture of the melanoma and are not obviously malignant, although they tend to recur after removal.

tilage and fat as well; Cushing and Eisenhardt assign separate types to each of these. Sometimes they may penetrate such bones

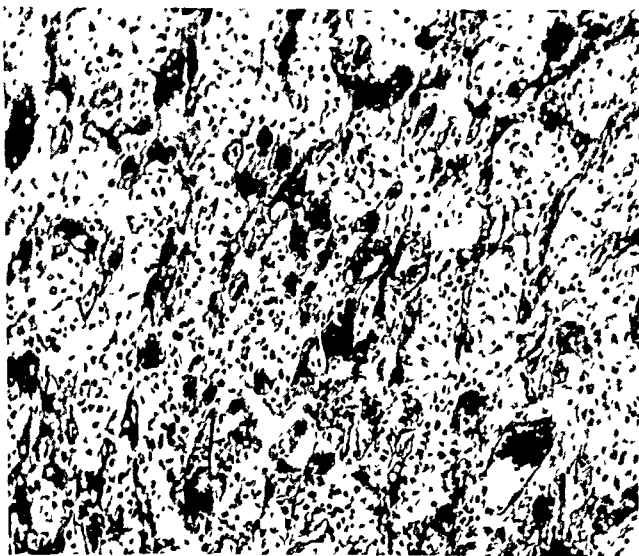


Two groups of meningeocytes invading medullary spaces of skull near an "osteoblastic" meningioma.

Microscopically they may be divided into a number of types, but this seems to be unnecessary, as the differences lie chiefly in the grouping of the elements, the amount of fibrous tissue present, and like distinctive nuances that strike one as a little artificial.



Hemangiosarcoma of meninges of cerebellum, part of which is seen at left. Black masses at right are engorged meningeal vessels. Cells of tumor surround them. These are small and stellate and may be either adventitial or neuroglial in origin.



Meningeal hemangioma simulating perithelial or "gemmangiomatous" type of hemangioma seen elsewhere in the body. Note marked proliferation of perivascular adventitial tissue. This is a rather common meningeal tumor and is not malignant.



Arachnoid type of meningioma Note whorls that resemble arachnoid villi and the fact that this particular tumor contains pigmented cells in its stroma.

as the ethmoid and appear in the nasal cavity, where they are apt to be misdiagnosed. When they occasion thickening of the overlying cranium one will find small islets of meningeal tissue in the haversian systems of the bone.

Cushing and Eisenhardt include a group of vascular tumors of the meninges which would better, it seems, be classified as me-

outside of the cord and, by exerting pressure upon it, produce transverse myelitis. Removal of the "tumor" reveals that it is a typical Hodgkin's granuloma of lymphoid tissue.

TUMORS EXTRINSIC TUMORS There are many tumors which may affect the bone, cartilage, remnants of the notochord, and vascular tissue, and by their presence these compromise the spinal cord either by pressure or by actual invasion. Metastatic carcinomas of the vertebrae may break out of these into the spinal canal and invade the nervous tissue. Those of the prostate not infrequently do so.

We have discussed meningioma in the preceding pages, as well as medulloblastoma and melanoma, all of these may affect the meninges of the cord as well as, or instead of, those of the cerebrum and cerebellum.

INTRINSIC TUMORS These are excellently discussed in two papers that have appeared within the last few years, one is by Kernohan, the other by Rasmussen, Kernohan, and Adson. The first is a general review of the subject from which the following facts may be gleaned. Kernohan finds that one out of every five tumors of the central nervous system occurs in the cord. They are most commonly located in the thoracic segments, and fortunately they are apt to occur on the posterior surface, where they are accessible to the surgeon, rather than on the anterior surface, where they would be more difficult to eradicate. The commonest types are meningiomas and neurofibromas (types that we either have just discussed or shall take up very soon in connection with the peripheral nerves). Tumors of the cord in general occur most usually in the middle years of life, and 70 per cent of them fall into three main categories: meningioma, neurofibroma, and intramedullary tumors. The rest belong in the extrinsic group that has just been briefly touched upon.

INTRAMEDULLARY TUMORS Kernohan points out that astrocytes are less commonly found in the cord than in the brain, while ependymal cells are more numerous

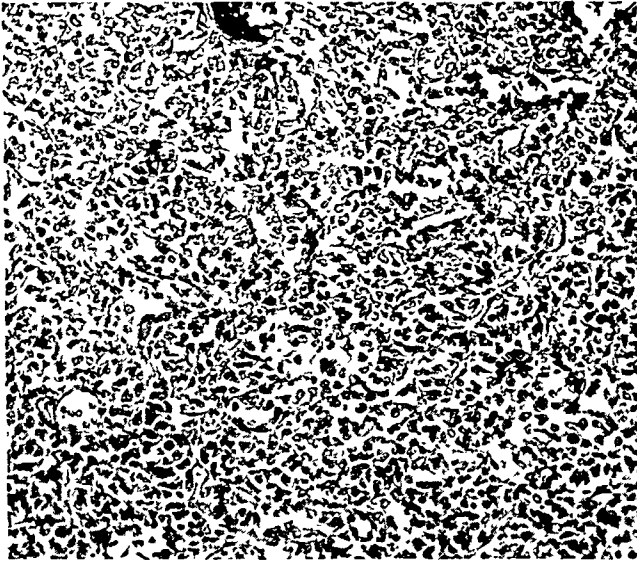
and extend throughout the length of that structure in its core. Hence astrocytic tumors are naturally less common than in the brain, while ependymal growths occur more frequently. The breaking up of the central canal, with many interruptions of its continuity as development proceeds, displaces many ependymal cells which then tend to wander into the surrounding gray matter and constitute groups which are potential nuclei for neoplasms. Ependymal cells become conspicuously scattered in the filum terminale of the cord in the region of the *cruda equina*.

In reviewing 557 cases of tumors of the spinal cord, Rasmussen, Kernohan, and Adson discovered that 64 were intramedullary. Of these 30 per cent were cervical, 61 per cent thoracic, and 9 per cent lumbar. There were 32 additional examples of glioma of the filum terminale, combining these with the above the resulting total of 96 tumors revealed a percentage of 67.7 per cent of ependymal growths, 10.5 per cent of astrocytic tumors of various types, 3.1 per cent each of oligodendrogliomas, glioblastoma multiforme, and medulloblastomas, 2 per cent of neuroblastic neoplasms, 5.2 per cent of hemangio-endotheliomas, 3.1 per cent of primary "melanocarcinomas," and 1 per cent each of fibrolipomata and neurofibromata. Foerster and Bailey reviewed the literature on these tumors in 1936 and found 100 cases, reporting some of their own in addition. They state that 50 per cent of the growths reported in the literature are ependymomas.

It will be unnecessary to describe these tumors more minutely, as they are essentially similar to those found in the brain. It should be pointed out, however, that the percentages of occurrence are interesting. Most of the tumors are the relatively slow growing ependymomas, while in the series we have quoted only 5 per cent are the dread glioblastoma multiforme. Of Foerster and Bailey's seven tumors, only one was of this type. The reason for this reversal of frequency of incidence has been indicated above: in the cord there is not the vast

The melanoma (which will be described later on) metastasizes early and has a quite different histologic composition. Pigmented meningiomas are jet-black, spread over the meninges like ink blots, and may be multicentric. Aside from the melanin they contain they have the structure of the arachnoid type of meningioma.

Prognosis and Treatment. As a rule meningiomas have a relatively good prognosis



Meningeal angioblastic sarcoma which is very cellular and, in this case, exclusively composed of angio-endothelium.

if they can be completely removed by surgical operation; unfortunately they are apt to grow rather diffusely and to be poorly delimited, so that the surgeon should leave as wide a margin of safety behind him as possible and excise widely. Irradiation is of no avail.

MELANOMA. This tumor will be described at length in connection with the peripheral nerves, but when it occurs in the meninges it apparently originates in bodies similar to the Meissner's corpuscles of the skin—tactile organs that have been studied carefully by Masson, among many others. Here in the meninges they may appear quite independently of any cutaneous melanomas and form black tumors that may penetrate the brain or cord and arise in a multicentric fashion. Microscopically they have the ap-

pearance of the cutaneous melanomas. They are malignant, and (in one instance necropsied by Zeek and reported by her and myself) may show widespread metastases in the lungs. As is so often the case in melanomas elsewhere, the production of pigment varies from tumor to tumor, and some may be jet-black while others show scarcely any pigment.

SPINAL CORD

The spinal cord combines the structure of the organ we have just been considering, the brain, with those we are about to take up, the peripheral nerves. In other words it consists of a central core of tissue similar to the gray matter of the brain and a peripheral portion that is composed of tracts of nervous fibers. The latter are very much like peripheral nerves in so far as their pathologic conditions are concerned. Thus the spinal cord combines the chirurgicopathologic features of the brain with those of the peripheral nerves, both of which are considered in detail. This necessarily leaves comparatively little material for an extended discussion of the spinal cord's pathology, of which its neoplastic lesions are the most distinctive feature, its inflammations being relatively unimportant and its degenerations, while striking and of great interest to neurologists, being of even less importance from the standpoint of surgical pathology.

Infectious Granuloma. Tuberculosis of the vertebrae may involve the spinal cord, or it may arise in the meninges thereof, or it may produce solitary tubercles here, as in the brain. These tubercles may produce signs and symptoms readily mistaken for those of neoplasms. Syphilis may also give rise to gummas of the cord, which will resemble the solitary tubercles; the commonest lesions due to syphilis, however, have to do with such diseases as luetic meningitis, tabes dorsalis, multiple sclerosis, and other such manifestations of cerebrospinal lues which do not concern us here. Hodgkin's disease may affect intraspinal lymphoid tissue

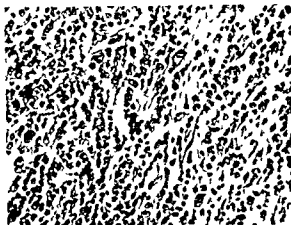
the cells of Schwann, others that combine these with concomitant overgrowth of fibrous tissue of mesodermal origin, and a group (closely related to the schwannian tissue) that forms pigmented tumors or melanomas representing distortions of tactile corpuscles and end organs

NEUROMA Neuromas may be divided into groups according to their degree of differentiation. They appear to originate in cells that migrate from the neural crests, and their various forms are indicated in Chart III

Sympathogonioma The medullo epithoma of the central nervous system has its analogue in the peripheral nerves—the sympathogonioma, which is a rare tumor found along the distribution of such nerves as the ulnar, median, tibial and the like. It was first described by Cohen and often goes under his name. Not as a rule very large, it is fairly well encapsulated, and under the microscope it proves to be made up of gland-like rosettes of primitive neuroblasts or “sympathogonia.” It has been reported in an intercostal nerve by Andrus, and Marchand described a classical case in the suprarenal gland which puzzled him for a long time, in a later article he named it a “neurocytoma” and initiated considerable confusion in the ensuing years. The tumor is decidedly peculiar, youthful, and undifferentiated, and it is academically malignant. One hesitates to advise treatment, as so few have been documented that we have very little experience in the matter.

Sympathoblastoma (*Sympathicoblastoma*, *Neuroblastoma*) Not at all a rare growth, this is usually seen in children and originates in the neighborhood of the suprarenals or actually within them. It corresponds in many respects with the medulloblastoma of the central nervous system, and like that tumor it may exhibit two potentialities—a neuroblastic and a spongioblastic one. In the early days of pathology it passed as a lymphosarcoma, but it was taken out of that category by Wright in 1910, he named it “neuroblastoma”—a term by which

it is still largely known. It is a very malignant growth that metastasizes so widely as to appear almost multicentric, if it arises on the right it invades the liver and then spreads to the lungs and the body in general, if it arises on the left it bypasses the liver, metastasizing directly to the bones and lungs and being prominent in the cranium. The former type is clinically known as the “Pep-per type,” the latter as the “Hutchinson”



Neuroblastic sympathoblastoma metastatic in a lymph node. Note large pseudorosette at center of field. There are vague fibrils in its center. Less well-formed rosettes are visible elsewhere in picture.

In the skull it causes punched out defects exactly like those noted in the case of leukemic chloromas, from which it must be diagnosed. These are filled with spheroidal masses of soft, readily compressible, and more or less hemorrhagic neoplastic tissue that is translucent and white on section.

The microscopic picture is characterized by small lymphocytoid cells having slightly more cytoplasm than do the lymphocytes, which in some examples may be slightly drawn out into poles to create blunt fusiform or actually fusiform cells. With silver impregnations on frozen sections one may differentiate between neuroblasts and spongioblasts in the growth, the former impregnating densely black, with the exception of their nuclei which stand out as paler areas. The latter take a much less intense impreg-

reservoir of precursors of astrocytes that is encountered in the brain, while the opportunities for ependymal proliferation and aberrance are correspondingly better.

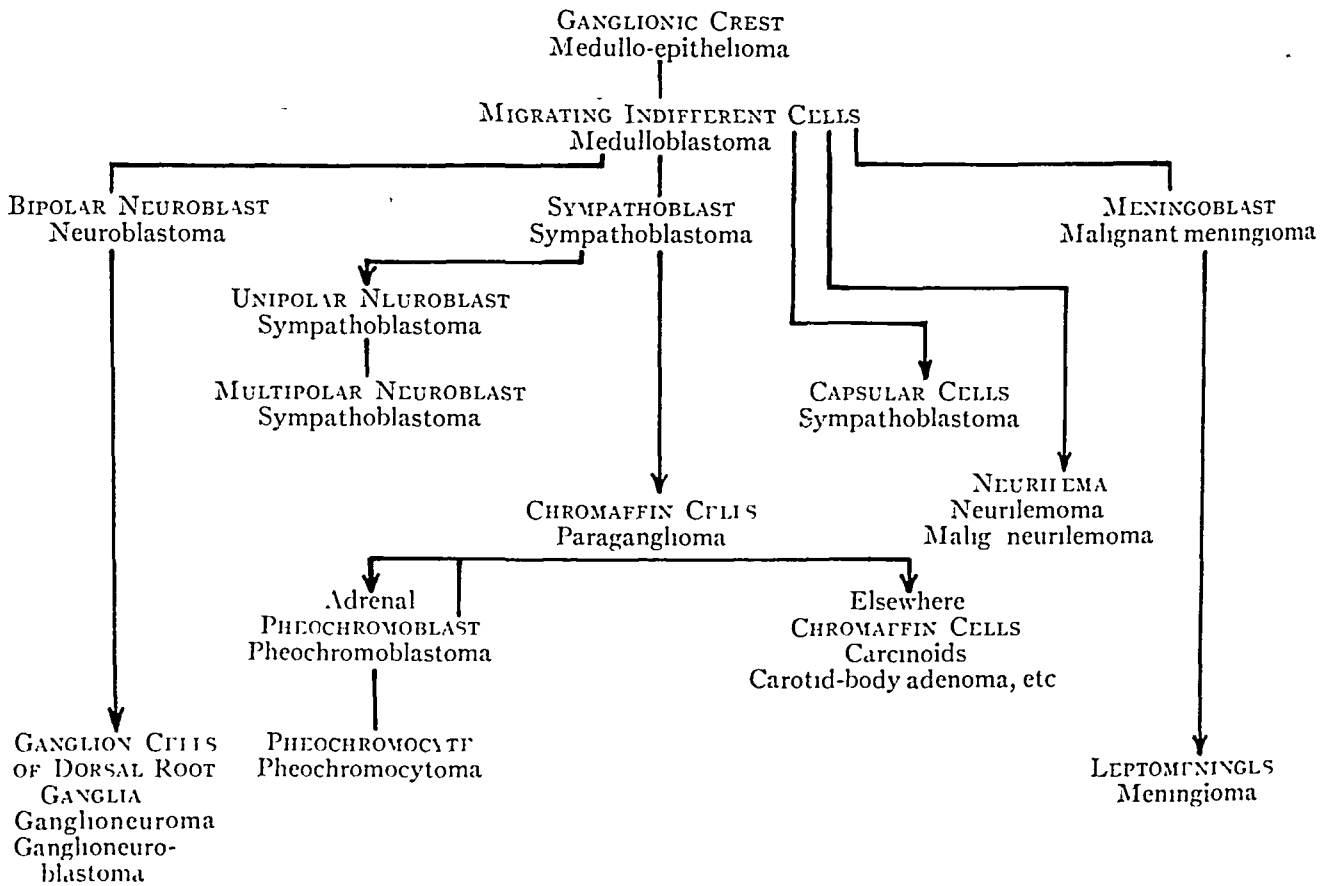
PERIPHERAL NERVES

Tumors. Not long ago the writer published a proposed classification of these tumors based upon the histology of the peripheral nervous system. This is indicated in Chart III taken from Bailey and Cushing's much-quoted book. There have been many classifications since Virchow first called these tumors "neuromas," and a good deal

traditional definition of what constitutes a neoplasm. For that reason it would be better to call such proliferative knots of neurofibrils "pseudoneuromas." The traumatic factor is evident in the case of the "amputation neuroma"; it is inferred in that of the fibrillary pseudoneuroma that is usually found upon the dorsum of the hands where trauma is frequent and often unnoticed.

One should, then, recognize neoplasms of neurocytes connected with peripheral nerves, those of the cells of nerve-sheaths (which are probably of ectodermal origin), and those of fibroblasts in the fibrous sheaths

CHART III



of confusion has resulted from the variety of names used and the variance of opinions as to the origin of the type-cell involved in certain tumors. Many so-called "neuromas" (the amputation or traumatic neuroma and the "fibrillary neuroma") are not really neoplasms. To call the proliferation of the processes of cells which may be quite normal and situated a matter of feet away from this proliferation a "tumor" is to upset the

of the nerve trunks which are similar to ordinary fibromas and fibrosarcomas, although there is evidence indicating that these cells are slightly different from those of collagenous connective tissue in general. Thus we shall have to deal with tumors of primitive neuro-epithelium, others arising in cells of the order of medulloblasts and (under normal conditions) situated in the sympathetic ganglia, growths derived from

PLATE V



Kodachrome photomicrograph of field from meningioma showing a psammoma ("sand tumor") granule or body in color. Masson's trichrome stain was used.

nation. Various types of sympathoblastoma may be recognized and rather complicated subtypes distinguished on the basis of the degree of differentiation of the cells. Reference to Chart III will explain how this might be effected, but it seems better to lump all these forms into the single category of sympathoblastoma, as few of them are pure examples. This has been done in the schema.

The prognosis in a proved case of sympathoblastoma is quite hopeless. The growth does not respond to irradiation with x-rays or radium (even if one could implant radon seeds in all the tumors), nor is surgery of avail, because not all of the numerous tumors could be removed.

Pheochromoblastoma. This is derived from the pigmented cells of the paraganglionic tissue; when it occurs in the medulla of the suprarenal or in misplaced suprarenal tissue it is known as a "pheochromoblastoma" in its malignant form or as a "pheochromocytoma" in its better-differentiated one. If it arises in the intestinal tract, the carotid body, or other such structure it is known as a "paraganglioma." It is a brownish tumor which may grow to several centimeters in diameter and usually shows good encapsulation. Those of suprarenal origin may secrete pressor substances and cause paroxysmal hypertension. All of these growths exhibit an affinity for the salts of chromium and silver, hence they are also known as "chromaffin" or "argentaffin tumors." They have a microscopic architecture that vaguely resembles that of the carotid bodies, their cells are arranged in alveolar groups separated by a delicate stroma, and the cells are pigmented with a yellowish-brown, granular material. Sometimes these neoplasms show a very glandular type of growth. They may be noncancerous or cancerous; in the latter the picture is more disorderly, the cells showing marked pleomorphism and mitotic activity.

The carcinoids of the intestinal tract have been described with that system, the paragangliomas of the carotid bodies under the organs of internal secretion, the pheochro-

mocytomas and pheochromoblastomas of the suprarenal in connection with that gland. They all show much in common. When they constitute separate, accessible tumors they should be removed surgically; they do not always metastasize, as is evidenced by the appendiceal carcinoid, but as the malignant forms may do so they should always be treated radically. Irradiation is not recommended for any tumor connected with the nervous system; usually it is just so much time lost, and it means unnecessary discomfort for the patient.

Ganglioneuroma. There are two types of ganglioneuroma, one of them well differentiated, self-contained, and common, the other poorly differentiated, infiltrative, and so uncommon that few pathologists ever see it. Ganglioneuromas may grow to considerable size, forming solid and rather fibrous-looking tumors that cut with considerable resistance. They may occur at any age and in either sex. They are light brown or silvery white, depending upon which tissue predominates, the cellular or the neurofibrillary or neuroglial. The two last are, of course, white, the neuroglial sometimes having a yellow tinge. These tumors may occur near the posterior spinal roots, arising partly within the spine, partly in the thorax, in which case they are constricted where they pass through the bony foramen and have an hourglass shape that causes them to be known familiarly as "hourglass tumors." (The hourglass form is not at all pathognomonic of ganglioneuroma, however, as neurofibromas and neurilemmomas may take the same shape in this situation.) The tumors have a fondness for the intercostal spaces and mediastinum.

Microscopically the noncancerous ganglioneuroma is an organoid and highly differentiated tumor that shows a mass of neurofibrils, neuroglia, and (embedded at various points in these) groups of ganglion cells with their capsular or satellite cells. The proportions of these elements differ with different tumors; some of them may exhibit myriads of ganglion cells, others

only a few groups scattered through the nervous tissue of the stroma or matrix. The cells may be specifically stained by the



Field from ganglioneuroma, showing groups of typical ganglion cells lying among bundles of neurofibers

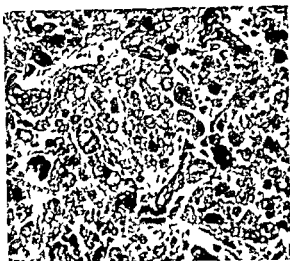


Cajal Nonidez impregnation of a ganglioneuroma showing neuraxones as black threads and ganglion cells as dark bodies with rounded or squash shaped outlines

Nissl method, with cresyl violet or brilliant violet to bring out the tigroid bodies, they may also be impregnated by the modified Ramon y Cajal silver method given in the chapter on technic. This method, which requires chloral hydrate fixation, will bring out the neurofibrillae and the delicate

basket work of these about the ganglion cells, some of which may exhibit impregnated axones.

The malignant form of ganglioneuroma looks exactly like the noncancerous type to the unaided eye, but under the microscope it will be found that there is almost total de-differentiation of the ganglion cells, which are converted into bizarre giant cells that

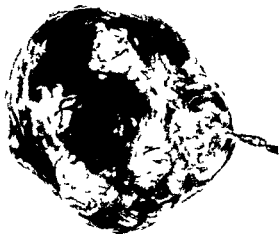


High powered field from ganglioneuroblastoma or malignant ganglioneuroma. Cells, impregnated with silver, are bizarre and distorted, they are also more numerous than those of the nonmalignant tumor, ganglioneuroma

resemble those of a sarcoma. They have lost their Nissl granules and processes and have rounded up to form quite atypical cells that would be hard to recognize were it not for the fact that a few of them may differentiate very well and thus be recognizable for what they are. Transitional forms complete the identification. Although they are a form of neuroblastoma, on account of their reversion to an undifferentiated and hence embryonal type of cell, they are seldom called this. Robertson, who first described them at length, called them "ganglioneuroblastomas." They metastasize and comport themselves like other malignant tumors.

Reviewing this subject in 1940 it was possible to find only seven or eight reports of this tumor, including one we observed at

troduced this spelling Masson has called the tumor a "Schwannoma," which is not a desirable term as it combines a German patronymic with a Greek ending. Prior to this it was known as a neurinoma, later as a perineural fibroblastoma. Penfield still calls it by the last name. It is a more common tumor than one might think and is only beginning to be accurately diagnosed,



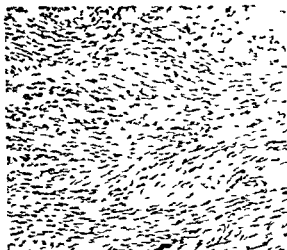
Photograph of large neurilemoma of mediastinum. The tumor was bright lemon yellow with reddish mottling.

one of its varieties possesses strikingly characteristic cellular arrangements that are readily recognized, but the other variety is rather nondescript and myxomatoid in its appearance. Evidence is accumulating that the more familiar neurofibroma may represent a scirrhous form of neurilemoma.

The neurilemoma is usually perched upon or embedded within a nerve trunk with which it is so intimately blended that it may be moved laterally beneath the integument but not up and down in the vertical axis of the nerve to which it is attached. This is diagnostic of tumors of nerves. It is yellowish, succulent, and usually very hard; it may resemble a rather moist and mucoid lipoma or liposarcoma or even a myxoma when examined with the unaided eye. Neurilemmomas are usually not very

large, averaging about 2 or 3 cm in diameter, but they may grow to considerable size on occasions. Those in the mediastinum are usually larger than those upon nerves of the extremities; in New York Hospital we have seen one that arose in the fatty capsule of the kidney and was $10 \times 8 \times 6$ cm or so in measurement. Such a tumor as this is readily mistaken for a liposarcoma. Neurilemoma shows a definite predilection for the acoustic nerve, where it is commonly called "acoustic neurinoma, or neuroma." It is a frequent participant in the multiple incidence of neural neoplasms in von Recklinghausen's neurofibromatosis, particularly in the case of those that affect the cranial nerves and the roots of the spinal nerves.

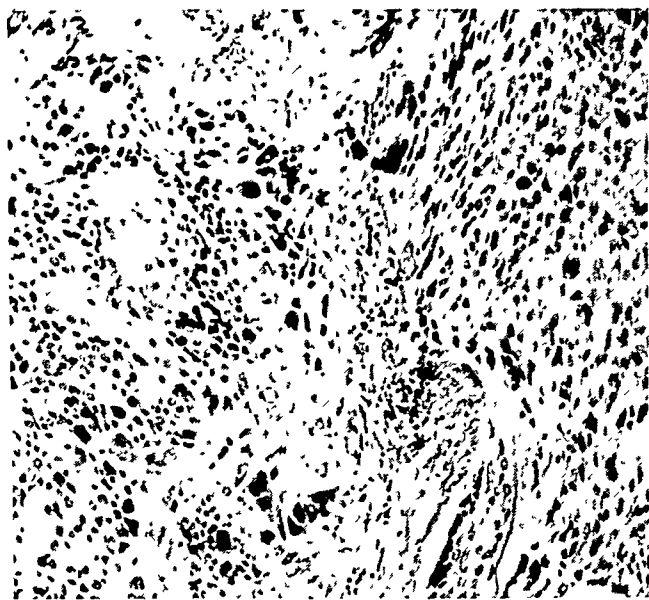
Before the neurilemoma's histology is discussed it would be well to sketch what is



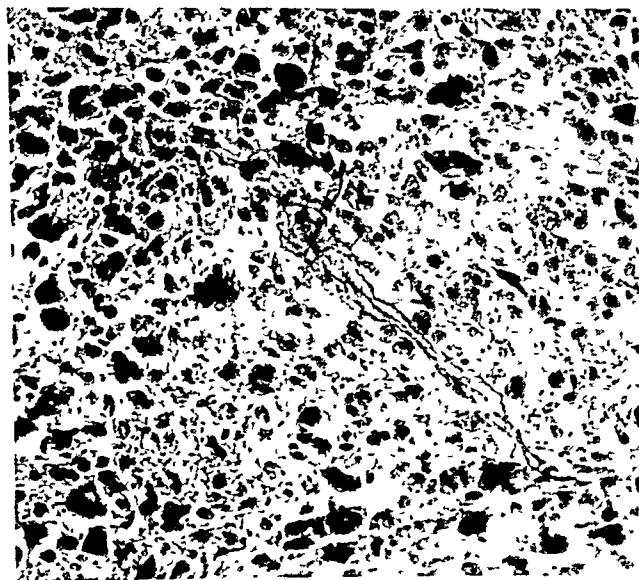
Antoni type of neurilemoma from acoustic nerve ("acoustic neurinoma"). There is a suggestion of incipient Verocay bodies here and there where nuclei are palisaded into rows.

believed concerning its histogenesis. There is still considerable dispute as to the origin of these tumors: one group considers them to be of ectodermal origin, offsprings of the neural crest, while the other as stoutly maintains that they are fibromas and mesodermal. Experiments have shown that the removal of the neural crest from tadpoles will result in failure of development of

the New York Hospital. In the latter case the patient, a child of two, unfortunately died of pneumonia four months after the



Ganglioneuroblastoma or malignant ganglioneuroma. This shows little resemblance to the comparatively orderly ganglioneuroma, as its cells are poorly differentiated and its architecture quite indefinite.

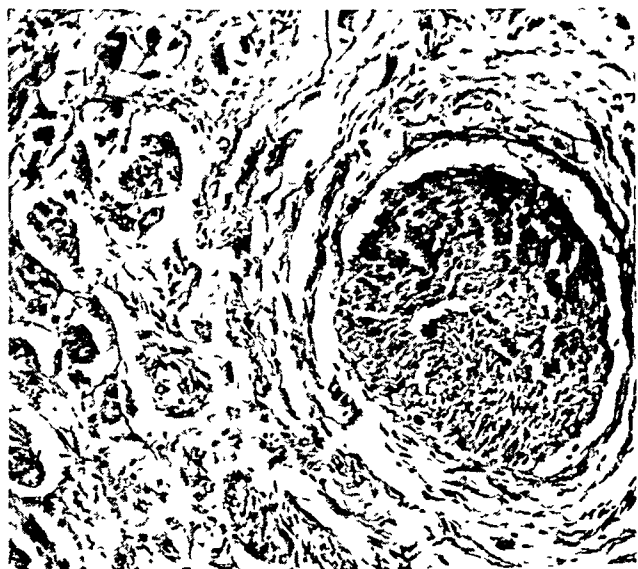


Poorly arranged neurofibrils in ganglioneuroblastoma. They are not only disorganized, but relatively scanty in number as well.

removal of the intraspinal portion of such a tumor, having recovered from the operation and been in good health until the infection supervened; we were thus unable

to complete the removal or observe the behavior of the remainder of the tumor.

TUMORS OF NEURAL SHEATHS. *Fibrillary Pseudoneuroma.* As has already been stated, it does not seem that the so-called "tumors" comprised in this group are true neoplasms. They consist of coiled nervous trunks and proliferating neural sheaths containing axis cylinders and usually developing after trauma. The most common is the



Field from an "amputation" or traumatic neuroma. Note large persisting nerve trunk and numerous proliferative pseudotrunk.

"amputation" neuroma that develops about the end of a severed nerve like the popliteal after amputation of the limb it served. This proliferation may also follow a blow over a nerve. Masson has written of an "appendiceal neuroma" which is composed of proliferated fibers from the plexuses of the appendix that may replace the lumen after its obliteration by a chronic inflammatory process.

Neurilemoma. Stout has given this name to a tumor that arises from the cells of the sheath of Schwann and constitutes an important variety of peripheral glioma. The more usual spelling would be "neurilemmoma," with two m's, but investigation of the derivation of the word proves it to come from the Greek stems for nerve (neuron) and sheath (ulema), therefore Stout has in-

esses often terminate in small bulbous enlargements Stout and Murray have grown these in tissue cultures and find that they differ in most respects from fibroblasts

In the Antoni type, the tumor is more like a myxoma in its microscopic composition, being made up of leucocytes and loose mucoid tissue that, again, stains pinkish with the Masson stain This tumor is much less ordered in its appearance than the



Antoni (Type II) form of neurilemoma from a nerve in thigh It lacks Verocay bodies that typify Type I

Verocay type and may often suggest a sarcoma, as it contains many large, roughly fusiform cells with correspondingly large nuclei which suggest neoplastic giant cells Neurilemmas are usually readily accessible to surgery and should be removed on account of the fact that they sometimes become transformed into the next type to be discussed X-ray is of no use at all

Malignant Neurilemoma One occasionally finds examples of neurilemoma that exhibit pronouncedly malignant characteristics, metastasizing and revealing a microscopic picture that is an exaggeration of the Antoni type, but even less definite in its architecture and replete with abnormal, neoplastic giant cells and mitoses Several of these have been reported If they can be removed soon enough by surgical operation this should be attempted Their manner of

metastasis is not particularly characteristic, but they may metastasize widely

NEUROFIBROMA A relatively common tumor, this develops in much the same situations as does the neurilemoma, but it is more fibrous and firmer and whiter In von Recklinghausen's multiple neurofibromatosis a patient may have hundreds of these tumors, of all sizes, scattered over and throughout the body and involving nerve-trunks, their spinal roots, and their subcutaneous twigs In conjunction with these there may be pigmentation either of the tumors themselves or of the overlying skin, this is nowhere intense enough to rival that of the melanoma, however Further to complicate the picture, other tumors such as fibromas, lipomas, and growths in the central nervous system may develop with the neurofibromas Hypertrophy of the sebaceous glands all over the body (Pringle's disease) may still further add to the confusion The patient is studded with knobby, pendulous, or fixed tumors until he resembles a barnacled post The tumors may also develop into huge apron like masses that hung down over the face, or over a flank, like large flaps, these are the "Ran-kenneurom" ("tendrils neuromas") of German medical literature

The microscopic appearance of the neurofibroma is one of coiled nerves in a dense fibrous matrix or stroma, but when the "nerves" are examined closely they are found to be mere empty neural sheaths without the axones All of these sheaths, naturally, are composed of leucocytes which constitute a large part of the tumor There may be abortive Verocay bodies in some of these growths, but they are never characteristic and readily pass unnoticed

NEUROGENOUS SARCOMA This is the malignant analogue of the neurofibroma, and when it develops from the fibrous tissue in the sheaths of nerves it is properly a sarcoma, but should it come largely from the leucocytes this term would be technically incorrect, if we adhere to the theory that those cells are of ectodermal derivation

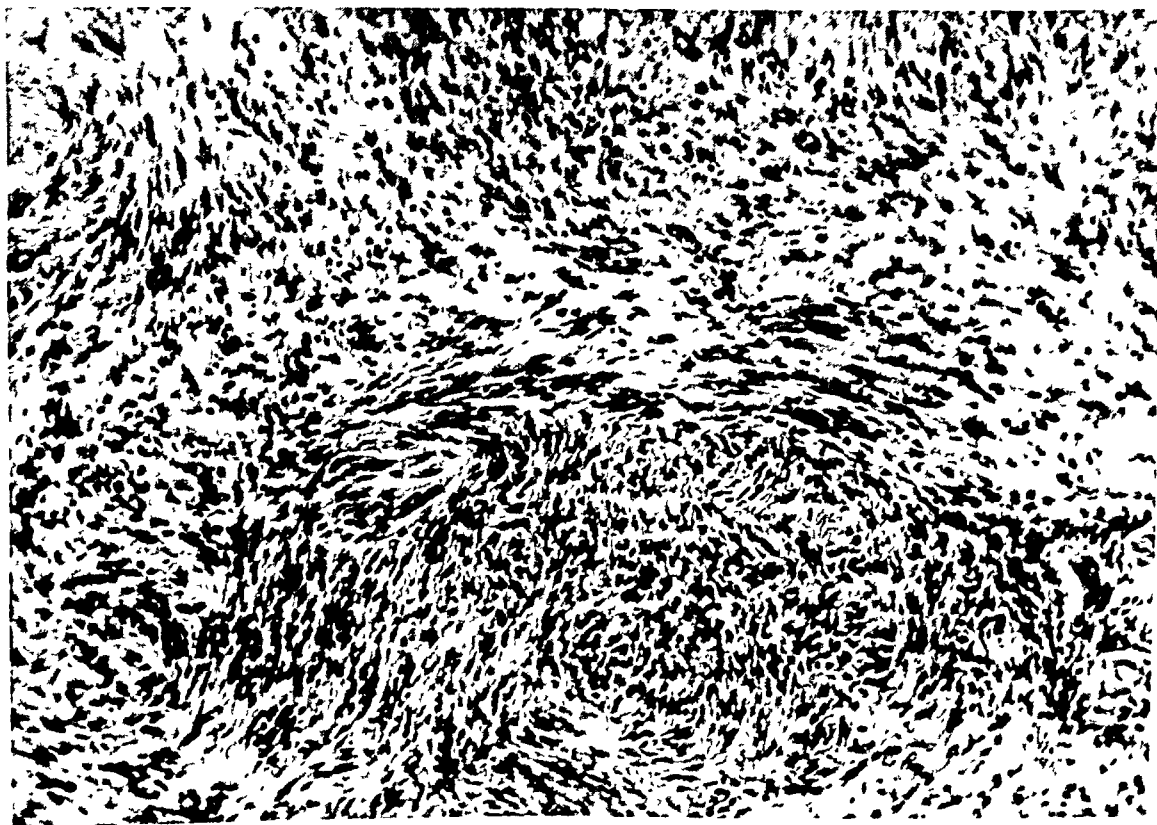
neural sheaths. Harvey and Burr, who conducted these tests, were sharply challenged and repeated their experiments on warm-blooded animals with the same results. This should be sufficient evidence to prove the ectodermal ancestry of these sheaths and of



Typical "Verocay body" from neurilemoma of a laryngeal nerve. Note parallel rows of palisaded nuclei and bands of hyaline collagenous fibrils that stretch between them, forming meandering, ribbon-like zones.

tumors derived therefrom; the references at the end of the chapter will indicate ample sources of information on both sides of this question.

There are two histologic types of the tumor: the Verocay, or Type I, and the Antoni, or Type II. The former is characterized by the presence of "Verocay bodies" which show parallel and opposing palisades of nuclei with fibers that are apparently fibrous tissue stretching between them from one palisade to the other. That these are ordinary collagen is commonly believed, because they have the staining reactions of that substance, but it is possible that this may be misleading. The palisades may be straight and like two football elevens in a line-up, or the bodies may show sinuous palisades contained within nodules that constitute thickenings in the matrix of the tumor, which is otherwise composed of loose fibers that stain pink and not green with Masson's stain and show cellular components that are essentially spherical with two polar processes which are attenuated, rather than fusiform or triangular like fibroblasts. The proc-



Neurilemoma of cauda equina in which Verocay bodies are rather poorly developed.

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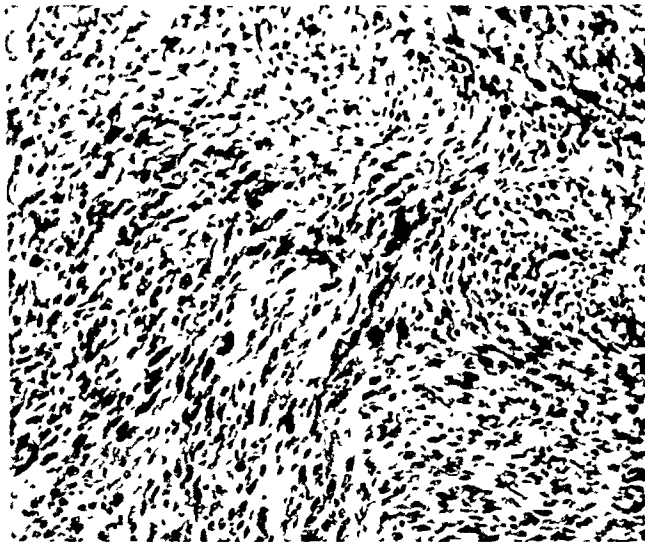
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These tumors usually occur along the course of nerves, often near joints, and when they are first removed surgically they may appear to be relatively innocent. When they recur, as they are certain to do unless widely excised, they will probably show more differentiation. It has been found that they should not be tampered with and removed with each recurrence, as they will become more and more malignant and ultimately



Neurogenous sarcoma of thigh: a malignant tumor arising in cells of neural sheaths (not Schwann cells) and mimicking fibrosarcoma, which is less whorled or fascicular.

metastasize and kill the patient. A second recurrence is a sign that radical surgery is called for, as has been proved by statistical study.

Because he believed that diagnosis based upon sections stained with hematoxylin and eosin was insufficient evidence of neurogenous origin, Stout has maintained the necessity for documenting the diagnosis by employing more specific methods, such as impregnation with silver or the use of Masson's or other trichrome stains. The microscopic appearance of such tumors varies from that of a fairly cellular fibroma with a very stellate, radiating, or "curly" architecture to examples that show marked metaplasia, neoplastic giant cells, many mitotic figures, and hyperchromatic nuclei. The matrix of the tumor will stain green,

not pinkish, with Masson's stain; this differentiates it from a malignant neurilemoma. The less malignant-looking tumors should call for careful reference to the case history in order to determine recurrence, situation, and so on. They should be carefully scanned for evidence of malignant change, as some of them are deceptively innocent at first glance.

TUMORS OF NEURAL TERMINALS. *The melanoma* is the most important of these; it may take the form of the usual congenital pigmented nevus or "mole" or that of the devastatingly malignant type most properly called "malignant melanoma," popularly known as "black cancer." Nonmalignant melanomas may be found anywhere on the skin as small brown areas; sometimes a very few will be present and sometimes they will be so numerous as to be disfiguring. They may be intra-epidermal and constitute pigmented spots (the French "*taches pigmentaires*"), or papillary and associated with wart-like overgrowth of the covering epidermis. They may form wide sheets of discoloration so as to cover large areas of skin (as is the case with the "*bathing-trunk nevus*"). They are a possibility in any region where tactile corpuscles might be found, so that we sometimes find them in the anal canal (where they simulate strangulated hemorrhoids), in the meninges (q.v.), or even in the penile urethra. If congenital, small, and not liable to irritation from clothing or occupation, and if they show no tendency toward rapid growth, they are almost invariably innocent; if, on the other hand, a quiescent nevus begins to grow noticeably, or if one develops suddenly and rapidly where none was hitherto seen, or if the nevus is very poorly outlined and black, they may well be malignant and appropriate steps should be taken for wide excision. Section through a pigmented mole will reveal that the pigmented portion is very superficial and that the tumor does not extend outside of the skin.

The histology of melanoma varies a good deal; the typical growth exhibits nests of

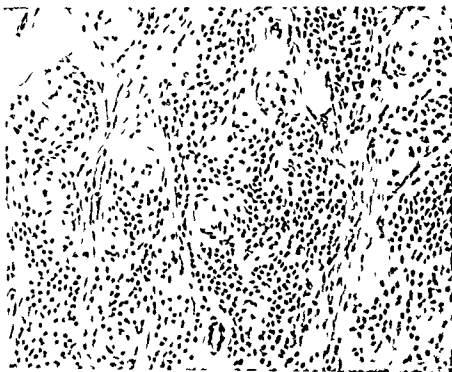
small, well differentiated cells grouped into clusters beneath the epidermis in the dermal papillae from which the Meissner's corpuscles have invariably disappeared. Each cell is surrounded by reticular fibrils, this differentiates the apparently dermal tumor very sharply from true dermal epithelium, in which the cells are in contact and no such fibrils are interposed. The amount of pigment demonstrable in microscopic sections is very variable, there may be much of it in the neoplastic cells, or it may be completely absent in the "amelanotic melanomas." This is an ungainly term, but for the present it seems to be unavoidable. Sometimes the cells of the nevus may be come multinucleated, which is not necessarily alarming.

The growths may be situated entirely in the basal layer of the epidermis, where they arise from the cells of Merkel and Ranvier; they may be very rich in neuroglial fibers and trunks that coil in the tumor and are not associated with many nevus cells. This is

known as a "neuronevus," and it is particularly prone to be found in the scalp. Sometimes the nests of cells show a peculiar whorled appearance and form bodies somewhat like the Verocay bodies of a neu-



Intradermal melanoma in which most of the neoplastic cells are in or near epidermis proper. A few superficial islets of cells have strayed into papillae.



'Neuronevus' of scalp. Note solid circular whorled structures (Masson's "lames foliacees") and strands of nonmyelinated nervous tissue. This is the type of tumor investigated by Masson and described in his classical article.

rilemoma; Masson has called these "lames foliacées." Occasionally the tumors may penetrate deeply into the derma and lie clustered about sweat glands and sebaceous glands.

The tumors often show a picture that combines that of melanoma with that of a verruca of either the "vulgar" or the sebor-

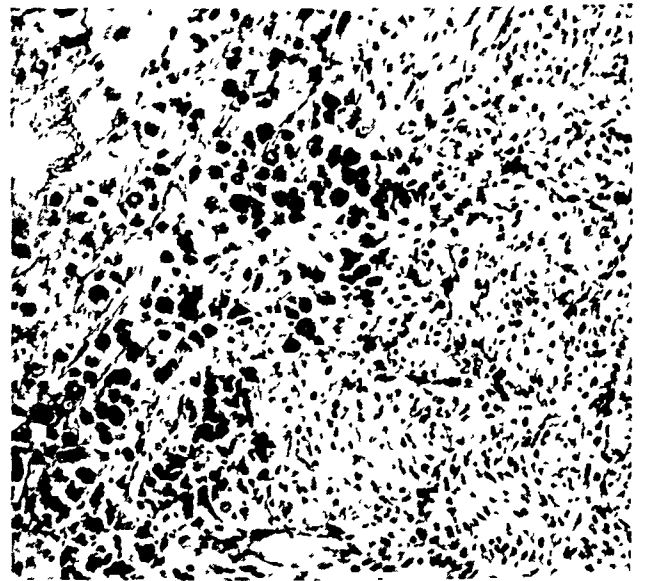


Dermal papilla invaded by malignant melanoma which shows fair differentiation but is invasive and actively growing. Epidermis of scalp above, nest of neoplastic cells below in dermal papilla.

rheic type. There is a form of pigmented tumor that departs radically from this type in that its cells lie grouped into spherical masses in the subcutaneous tissue or the lower corium. Its cells are deeply pigmented, large, and fusiform, and apparently they represent melanophores rather than melanoblasts. Lying deeply, they are seen as a blue spot through the overlying integument, wherefore they are known as "blue moles."

Malignant Melanoma. In this the microscopic picture is one of a disorderly overgrowth of large fusiform, ovoid, or polygonal cells that are deeply pigmented and more similar to those of the "blue nevus" than to

those of nonmalignant melanoma. There are also forms that occupy a position midway between the latter and those of the fully developed malignant melanoma. These evidence excessive clumping and general metaplasia and mitotic activity which, together with evidence of invasion of the subcutis, indicates early malignant metamorphosis. The outspokenly malignant tumors show one of two types: a sarcomatoid, composed of fusiform cells that tend to produce a complex like that of a fibrosarcoma, and a carcinomatoid type that is composed of more or less epithelioid groups of large, ovoid, pigmented cells. Before Masson traced the origin of the melanomas to the cells of Meissner's corpuscles (modified Schwann cells) these two forms were known respectively as "melanosarcoma" and "melanocarcinoma."



Metastasis in lymph node of malignant melanoma of leg. Some of its cells contain much melanin, others comparatively little.

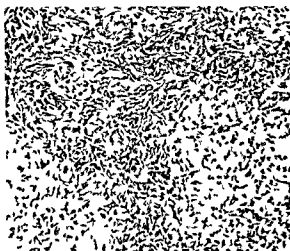
Malignant melanomas metastasize widely, usually by way of the blood stream, although lymphatic spread to regional and other lymph nodes may be noted. The tumor is apt to invade the spleen, which appears to be more or less immune to metastasis from most malignant tumors. Silver impregnations and the "dopa" reaction (dioxypheylalanine) may be of value in bringing out

the granules of melanin in the cells, as well as those containing its precursor, premelanin. It is said that the melanophoromas are dopa negative (Reference to Laidlaw's papers will explain the details of this reaction.) The metastases from a deeply pigmented malignant melanoma may vary in their content of pigment, some being as dark as the primary tumor, others being completely amelanotic, thus one may find a liver that resembles a plum pudding, literally riddled with black metastases, while the spleen in the same patient will contain white metastases that, at first glance, look like solid carcinomas.

"NEUROXANTHOMA" This tumor (to which this name has been given tentatively by the writer of this book) seems to be related on the one hand to the melanomas, as it often occurs just beneath a brownish spot in the skin, and on the other hand to the trunks of nerves, as these may be seen in proximity to the tumor. Furthermore, small nonmyelinated fibrils also may be demonstrated microscopically, running in the stroma among the nests of cells. These tumors are seldom larger than 8 to 10 mm in diameter, and they have a proclivity for the skin on the outer side of the thigh, although they may be found elsewhere. They are adherent to the integument and form stone hard nodules just beneath a brownish or bluish discoloration on the white surface. On section they are found to be sulfur- or orange-yellow and very firm and rubbery in consistence. The microscope shows them to be composed of nests of fusiform to ovoid cells arranged in a stellate radiating fashion about indefinite centers, so that the pattern is "curly." Between these cellular aggregations run rather stout trabeculae of connective tissue in which the neurofibrils are enclosed. The cells may or may not contain small granules or tiny vacuoles like those of the Touton cells of a xanthoma, if they do, the tumor is more orange in color, if they do not, it may be almost white. So

far as is known, these growths are usually nonmalignant, although an occasional dedifferentiated one with many mitotic figures and anisocytotic elements sometimes turns up.

Gross and Wolbach have described a "sclerosing hemangioma" that has almost the same microscopic and exactly the same



Section from yellow subcutaneous tumor variously known as "xanthoma, xantho granuloma, sclerosing hemangioma, and neuroxanthoma." Although its origin is disputed, its appearance is always like that of this illustration, and it exhibits a typical "curly" architecture with variable numbers of foam cells entangled in fibrous tissue.

macroscopic appearance. Their thesis is that the vascular channels of an hemangioma become compressed by overgrowth of the adventitial cells which take up lipoids and manufacture fibrous tissue which gives the tumor its hardness. Therefore the question is open to two interpretations, either of which seems reasonable enough according to the neurogenous theory the foam cells are altered schwannian cells, and the tumor thus is related to the neurilemoma, neurofibroma, and melanoma, according to the vascular theory the cells are derived from the perivascular adventitia and the growth is related to vascular tumors in general. As malignant forms occasionally present them

selves, it is advisable to remove the tumors with a wide margin by surgical operation.

PAINFUL TUMORS ASSOCIATED WITH NERVOUS SYSTEM. The glomic tumors of Masson have been discussed with the vascular neoplasms; they have a rich supply of nervous end organs and plexuses associated with the arteriovenous channels that constitute the tumor proper. Thus they are probably more properly vascular than nervous growths, and the excruciating pain that they occasion is attributable to the richness of terminal nervous organs about the vessels. These glomic tumors usually occupy a small part of the nail bed beneath the fingernails, although they may be found elsewhere. The other painful tumor is less readily connected with the nervous system, as it is a solitary leiomyoma that arises in the corium of the skin, apparently stemming from arrectores pilorum. It occasions pain that is out of all proportion to its muscular make-up; the microscope reveals no neurofibrils or terminal organs to account for this.

These two tumors, the glomic and the leiomyoma cutis, really do not belong in the category of tumors of the peripheral nerves. They are mentioned here merely because they both cause exquisite pain and tenderness that might mislead one into thinking that they were neoplasms of nerve endings.

TUMORS OF OTHER NERVE ENDINGS. Neoplasms composed of the elements of pacinian corpuscles have been looked for, but they have been described on one occasion only; this is cited by Ewing. That they are not observed oftener may depend upon two or three factors: they are very rare, and they may not proceed far enough with a characteristic differentiation into "onion bodies" to be recognized, so they are misdiagnosed when they do occur. One sometimes sees structures in neurofibromas that suggest pacinian corpuscles, and we have had one example in our laboratory that came from the scalp and closely resembled the only such tumor thus far described.

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retain their nuclei the condition is called "parakeratosis."

The skin is punctured at intervals by the ducts of the eccrine sweat glands that lie in the corium and by a variable number of hair follicles consisting of a hair shaft and the sebaceous glands that open into its sheath, the root of the hair lies beneath the epidermis in the corium.

The corium or derma is a loose mass of connective tissue which sends papillary projections into recesses in the epidermis, these papillae contain the vessels and the nerves that supply the skin. Many of the latter end in ellipsoids of modified Schwann cells about branching neural terminals. These structures are known as Meissner corpuscles, or tactile corpuscles. Between the papillae there are plugs of epidermis which project downward into corresponding recesses in the corium, so that epidermis and corium are dovetailed together by a series of papillae and depressions all fitted snugly together, with their close union assured by the reticular fibers already mentioned.

HISTOPATHOLOGY OF SKIN

This subject is important and voluminous enough to fill 500 pages of a book of quarto size or, in the case of some foreign publications, several large volumes. Therefore it is not our purpose to consider dermal lesions as carefully as those of other tissues have been considered, for descriptions of the rarer lesions the reader is referred to such textbooks as McCarthy's excellent publication. It often happens that the dermatologist can tell more about a given disease of the skin by observing it clinically and summing up his impressions than the pathologist can do by examining biopsies under the microscope. Many pathologic conditions of the skin have too much in common with others, when viewed microscopically, to make diagnosis definitive by that means alone, this should be carefully borne in mind during the ensuing descriptions.

Be that as it may, a surgical pathologist with a working knowledge of dermatologic pathology and the willingness to learn more by studying dermal lesions under the microscope with the dermatologist is always a welcome adjunct to any department of dermatology. In order to make histologic examinations of dermal lesions it is well to employ a small dermal trepan that will remove a cylinder of the integument through the surface and into the corium—a cylinder that will be about 4 mm. in length, with a diameter of the same magnitude. This cylindrical mass is then fixed in Bouin's solution, which is unsurpassed for fixing dermal tissue, as it does not harden it unduly, this solution's only disadvantage is that of obscuring the gross lesion on the epidermal surface for gross examination. Skin, particularly when hyperkeratotic, forms a comparatively unmanageable tissue when fixed in Zenker's fluid or formalin.

The stain is a matter of choice. Most pathologists content themselves with hematoxylin and eosin, but the Masson trichrome light green method is very advantageous. It stains keratin bright orange, the intercellular bridges of the stratum spinosum (malpighii) come out bright red, elastic tissue is reddish, and collagenous tissue green, so that one may estimate their proportions very easily. Inclusion bodies in the epithelium stain orange vermillion and are sharply set off from the rose pink cytoplasm of the cells. This is valuable, for example, in demonstrating the "corps ronds" of Darier's disease or the inclusion bodies of *molluscum contagiosum*.

Dermal pathology is usually studied and practiced by dermatologists, who have the advantage of having observed the lesions in situ on the body of the patient. They are also familiar with the clinical history of a given case, which is often withheld from the pathologist through errors in the filling out of the blanks that should accompany each specimen. The maintenance of a laboratory of dermatologic pathology is expensive, however, and often the volume of material

21

Skin

HISTOLOGY
HISTOPATHOLOGY
ATROPHY
HYPERTROPHY
VESICULAR LESIONS
INFLAMMATION
CHRONIC SPECIFIC INFLAMMATION
DERMATOMYCOSES
DERMAL MANIFESTATIONS IN LEUKEMIA
MYCOSIS FUNGOIDES

TUMORS
EPITHELIAL
EPIDERMOID
"BASAL-CELLED"
TUMORS OF DERMAL ADNEXA
CYSTS
OF SEBACEOUS GLANDS
OF SUDORIFEROUS GLANDS
OF CERUMINOUS GLANDS
TUMORS OF CORIUM

HISTOLOGY OF SKIN

The skin consists of an outer epithelial membrane, the epidermis, and a more or less dense layer of fibrous connective tissue, the derma or corium. The outer layer is bound to the inner by fine fibrillae of reticulum that run among the deeper layer of epithelial cells of the epidermis and thus anchor it to its substratum of connective tissue.

There are several recognizable layers of epithelium in the epidermis. Beginning at the bottom, we find a basal or germinal layer from which the others are developed by differentiation as the cells work outward toward the surface, from which they are constantly shed. The basal layer consists of somewhat columnar cells arranged in a palisade and regularly exhibiting a number of mitotic figures as new cells are produced to work their way out and replace those shed from the surface. Intercalated among the simple columnar basal cells are vacuolated elements which are not readily seen in ordinary histologic sections, but which stand out plainly in those stained by Masson's method. These are the cells of Merkel and Ranvier. They are often mistaken for degenerated elements, but in

reality they are considered to be terminals of fine nervous filaments associated with the tactile sense. The cells of the basal layer are more or less pigmented, being slightly so in blonds, more so in brunets, and very much so in Negroes; the color of the skin as a whole depends upon this thin layer of pigmented cells.

Next above the basal layer, or stratum germinativum, comes the mucous layer or stratum malpighii (also "rete malpighii" or merely "rete") which is broadest of all and composed of polygonal cells that are interconnected by intercellular filaments or bridges. When teased apart each cell looks as though it were surrounded by prickles or thorns, hence the terms "prickle cell" and "acanthosis." Cells in the outer layer of this stratum become stippled with a material that stains deeply with hematoxylin: this is the granular layer or stratum granulosum. Between this and the next stratum is a narrow band of pale squamous cells, the stratum lucidum, and over it is a thickish stratum of cornified squamous cells, the stratum corneum. Thickening of the stratum malpighii is called "acanthosis," while thickening of the stratum corneum is known as "hyperkeratosis" or "keratosis." If the cells of a thickened horny layer

carcinoma The metaplasia is variable, it may be slight as in "Bowenoid" lesions or it may be frankly carcinomatous The collagen begins to stain like elastic tissue ("pseudo elastic tissue") that is coarse and packed into heavy strands and bundles

SCLERODERMA This is one of those diseases (discussed under the vascular system) in which the skin manifestations are only a part of the generalized disease It begins

there was formerly a rich inflammatory exudate one now finds sleeves of lymphocytes about the vessels Elastic tissue is relatively spared, but may occasionally be destroyed

The vascular changes are essentially those of a fibrous adventitis, each vessel becoming surrounded by layers of connective tissue that are two to three times the normal thickness of the adventitia and are infiltrat-



Section from skin in scleroderma The lesion is seldom any more spectacular than this one Note the almost acellular, densely collagenous corium and the atrophy of overlying epidermis

in the skin with a comparatively brief inflammatory phase in which erythematous, raised, and edematous patches form on the skin and rapidly pass over into the sclerosing lesion, in which collagenous connective tissue plays the stellar role Bundles of coarse fibers spread the papillae apart and ultimately wipe them out, so that the epidermis lies flat over the fibrosed corium, without the usual waving outline of its basal layer The epidermis is thin and membranous The fibrous bundles are not confined to the corium, but also involve the subcutaneous fat, replacing it and fixing the skin firmly to the underlying parts which, in the case of muscle, may also be invaded by the fibrous inundation The microscope reveals these changes, and where

ed by lymphocytes This may result in the obliteration of the lumina, or they may be as effectively obstructed by proliferation of the vascular endothelium Arteries and veins suffer alike, but the latter to a somewhat lesser extent The lesions are notably "spotty", some areas are intensely affected while others are relatively spared Thus the disease appears to be essentially vascular

Dermal Hypertrophies Many of the conditions listed as hypertrophies of the skin should, under some circumstances, fall into different categories Warts, for example, may be considered as (1) local hypertrophies, (2) viral infections (as yet unproved), or (3) tumors of an atypical, often regressive type Molluscum contagiosum, which McCarthy considers under the hypertrophies, is now a proved viral infection—

for examination is too small to justify this expense. Then the surgical pathologist gets his opportunity.

In outlining the histopathology of the commoner lesions of the skin McCarthy's arrangement of subject matter will be followed and abstracted, such additions or alterations as may be pertinent being made from time to time.

follicles are the most affected (a feature that is made use of in depilation of unwanted hair). The sudoriferous glands swell and become slightly and acutely inflamed. Edema of the corium follows; the elastic tissue succumbs and disappears and, much later, the collagenous fibers proliferate and produce the characteristic late lesions of "chronic x-ray dermatitis." All this presup-



Typical lesion of x-ray dermatitis demonstrating metaplasia of cells of rete malpighii with mitotic figures outside of basal layer (ectopic). There is some resemblance to the lesion of Bowen's disease.

The Atrophies. Two of these should be included here: (1) x-ray dermatitis, which is becoming increasingly common in patients treated during the past decade with the x-ray, of which the ill effects are beginning to appear; and (2) the systemic disease scleroderma.

X-RAY ATROPHY. The acute phases of this condition are not pertinent except in so far as they influence later changes; the first effect of the x-ray is to dilate all the dermal vessels and to swell the cells by causing hydropic degeneration. Atrophy and pigmentation of the epidermis follows, with a loss of rete pegs (the downward projections of the epidermis). Of the dermal adnexa, the hair

poses that the dosage has been therapeutic; destructive or "caustic" doses cause extensive necrosis and even sloughing of the skin.

In established chronic x-ray dermatitis the skin becomes similar to that of scleroderma, with a leathery corium and an altered epidermis. Ulceration does not appear until the circulation has been curtailed by fibrosis. Microscopically one finds the epidermis thickened and apt to show an increased stratum spinosum (or rete). The adnexa have disappeared and the papillae are irregular and distorted. The thickened epidermis may begin to exhibit localized areas of papillomatous growth that becomes increasingly metaplastic and presages x-ray

palms and soles into thick masses of horny tissue

Lesions Characterized by Formation of Vesicles There are a number of these that seldom occasion biopsies, many of them constitute the eruption of acute exanthemata like smallpox (variola) and chicken pox (varicella)

SALVARSAN DERMATITIS This is an arsenical rash that may simulate lichen planus, eczema, pemphigus, or urticaria. It is accompanied by loss of hair and nails and a general production of pustules. Microscopically the early changes are parakeratosis and edema of the cutis, the latter balloons out the papillae, which become irregular in size and shape. There is a slight perivascular infiltration by lymphocytes which may also be scattered beneath the epidermis in small numbers. Vacuolar degeneration of the cells of the stratum malpighi results in a loosening of its structure and the formation of intra epidermal vesicles. The epithelium becomes irregular, and some of its cells resemble neoplastic giant cells, although there is no mitotic activity among their fellows.

ECZEMA This is considered to be a disease of the epidermis and to depend upon special sensitivity to certain substances—a quasi allergic if not frankly allergic phenomenon. It exhibits acute and chronic phases.

Acute Eczema Patches of redness develop, becoming covered successively with fine scales, papules, and finally small vesicles which (if they develop under a thinly keratinized layer) may fuse to form small bullae or blisters. These keep bursting and wet the surface (hence the term “weeping eczema”). The lesions ultimately heal with the production of some thickening of the skin and the formation of scales. The process is in a constant state of ebb and flow, so that lesions in all stages of development and subsidence may be observed simultaneously.

Microscopically, the epithelium becomes edematous in the early stage and its cells swollen and resistant to staining, so that the sections look pale and one may blame the

technician. Leukocytes wander among the separated elements of the stratum spinosum. The horny layer shows areas of parakeratosis. Following this, the epithelium begins rapid proliferation and there is acanthosis and elongation of the rete pegs. A loosening of the epithelium precedes the formation of vesicles, and these soon become invaded by polymorphonuclear leukocytes and resemble pustules. Large vesicles may occupy almost the entire thickness of the epidermis. As the pustules break down they discharge their contents onto the surface and form crusts under the keratinized layer. Under these crusts a second horny layer may be produced, forming a characteristic sandwich like structure. The vessels of the corium are sheathed in lymphocytes, with neutrophil and eosinophil leukocytes among them.

Chronic Eczema (Seborrheic Eczema) This is microscopically characterized by an absence of the edema that was so characteristic of the acute form. There are several subtypes which we shall not consider here. The horny layer is either hyperkeratotic or parakeratotic to a slight degree, with scaly crusts and remnants of the pustular crusts of the acute stage imprisoned in its substance. Under the parakeratotic patches one may find edema of the rete malpighi as well as some cellular exudate. The papillae may be edematous and penetrate almost to the stratum corneum (a characteristic of psoriasis, as a rule). The vessels of the corium are surrounded by rather dense sleeves of lymphocytes and polymorphonuclear leukocytes. Eosinophils are often noted in the sections.

The psoriasiform variety of this disease resembles psoriasis both clinically and microscopically. It may be differentiated from the latter by the presence of imprisoned scabs, with remnants of leukocytes lying between nucleated cornified cells. Parakeratosis is not universal in the lesion and the papillae do not penetrate the epidermis as deeply as they would in the case of psoriasis. Edema of the papillae and the peri-

one of the few in which the inclusion bodies contain the active virus. Therefore it belongs with the chronic infections.

CALLUS (CALLOSITY, CALLOSITAS). This is familiar through the expression "the horny-



Section from clavus or common corn. Dense mass on surface is composed of keratinized epithelium. Below this is a typically irritated epidermis with plexiform rete cones which anastomose with one another. This is an almost invariable sign of irritation.

handed son of toil." A dermal callus is hard, yellowish to yellowish-brown, and results from the constant chafing of the integument by tools (e.g., the callus of the manual laborer's or golfer's hands). Callus also becomes an asset to violinists and harpists or players of other stringed instruments, protecting their fingertips from the cutting effect of the pressed or plucked strings. Callus also develops at the angle of the jaw of violinists, where they grip the instru-

ment. The microscopic picture is one of piling up of the horny layer into strata of dense cornified scales. There is some hypertrophy of the underlying stratum lucidum and stratum granulosum; below this there may be some atrophy, or no visible change in the other strata. Such callosities may become infected and show the effects of acute or chronic inflammation. A "corn" is a magnified callus, too familiar to need description; its center is of a denser consistence than that of the surrounding horny mass and forms a conical plug, with its apex directed toward the basal layer of the epidermis which it sometimes penetrates, impinging upon the nerve endings of the papillae. This plug is the "core" that is commonly softened and extracted by means of corn plasters.

CONDYLOMA ACUMINATUM. This has been described in connection with the urinary and alimentary systems.

THE KERATOSES. There is quite a variety of these; the more important will be described.

Follicular Keratosis. This is a hyperkeratosis of follicular openings or "pores" which are filled each with a small plug of dried horny material, beneath which is coiled the hair that has been imprisoned. The plug may be superficial, forming a ring about the orifice of the follicle, or it may be stouter and penetrate more deeply into this structure. The follicle may then become inflamed, or the imprisoned hair may work its way out of the sheath in a lateral direction and provoke a foreign-body reaction in the neighboring tissue. There is an infectious form of this disease in which the epithelium of the entire follicle becomes hypertrophic. As a result of either of these varieties, the sebaceous glands become atrophic as their outlets are stopped off. Several varieties of this lesion are recognized by dermatologists: some of them are rare, others depend upon slight variations on the theme just set forth.

Generalized Keratosis. Several varieties are recognized; there are palmar and plantar forms that run in families and convert the

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by causing local infection within the sebaceous ducts and in their supporting tissue, and this produces tiny localized abscesses which constitute the red pimple. Microscopically it may be noted that the abscesses in the follicles remain superficial and do not penetrate to the corium like boils or carbuncles. Discharge of a droplet of pus or the drying up of the small abscess by resorption terminates the process.

NEURODERMATITIS (PRURIGO VULGARIS) Biopsies are often taken from this rather common lesion. Its gross appearance reveals rather large plaques (2 x 2 cm or so in diameter) that are oval, triangular, or roughly rectangular and exhibit an outer zone of erythema, a midzone of excoriated and itching papules, and a central area of pigmentation and thickened skin. The microscopic appearance of the acute form is marked by edema of epidermis and corium, with dilatation of all the vessels, which are surrounded by sleeves of polymorphonuclears and lymphocytes. The moist middle zone shows infiltration of the epidermis by polymorphonuclear leukocytes, while in the central area there are scaly crusts. As the disease becomes chronic there is hyperkeratosis, and patches of parakeratosis are noted. The rete pegs are conspicuously elongated, so that they may form an anastomotic network with one another, like that seen in healing ulcers. There is increased pigmentation of the basal layer, and many melanophores may be found wandering in the papillae. These are phagocytes which take up surplus pigment from the melanoblasts of the basal layer. Acanthosis may become marked enough to produce verrucose projections on the surface of the lesion.

PSORIASIS This is a mysterious affection of the skin of the extensor surfaces and back that usually spares the flexor aspect of the extremities and the front of the body. Its cause is unknown, and treatment is notoriously unsatisfactory. It provides the surgical pathologist with numerous biopsies. The gross lesion is in the form of rosy and apparently inflamed papules and plaques

that become covered with silvery scales which, when removed, leave tiny bleeding points beneath them. The lesions may fuse until large irregular areas, like continents on a map, result ("psoriasis geographica").



Acute psoriasis "Air spaces" are appearing in epidermis, there is as yet little obliteration of the granular zone and no parakeratosis. These would appear later. There is a diffuse infiltrate of lymphocytes in lower layers of epidermis and an intra epidermal vesicle at upper right.

There may in some instances be wart like lesions with heavier scales, but the silvery, easily detached flake is more typical.

The microscopic picture has two outstanding features: there is great thickening of the stratum corneum, which retains its nuclei (parakeratosis), and marked penetration of the epidermis by outthrusting

vascular mantles of exudate are more prominent in eczema than in true psoriasis.

Acute and Chronic Inflammations of the Skin. **URTICARIA.** Commonly known as "hives," this is frequently encountered, and the pathologist should be familiar with it. The gross lesions are wheals of various sizes; they may be erythematous or reddened, and

bers of basophilic ("mast") leukocytes surround the vessels. The basophils are readily demonstrable with the Giemsa stain or with Nile-blue sulfate, and they are diagnostic. There is some acanthosis, and the upper layers of the epidermis may be somewhat thickened. If the lesion becomes very obstinate ("urticaria papulosa perstans") a



The rather nondescript lesion of neurodermatitis. Note diffuse cellular infiltration of corium (lymphocytes and polymorphonuclears); the swollen, elongated, and slightly infiltrated rete cones; and prominent stratum granulosum.

they itch intensely. They follow the ingestion of substances to which the patient is allergic, sea food and certain berries being common offenders. They are a frequent consequence of the injection of serum to which the patient has been sensitized in the course of the administration of antitoxins. "Urticaria" derives from the Latin name for the European nettle, contact with which produces a similar lesion.

The microscope reveals an intense acellular edema and possibly intra-epithelial vesicles. In the chronic papular form there is a marked cellular exudate in place of edema. Dense infiltrates of lymphocytes, a few lymphoblasts, polymorphonuclear leukocytes, and plasma cells, and large num-

ber of extraneous factors may be introduced by the patient's scratching and infecting the lesions. Here eosinophils are added to the catalogue of reacting cells. The epidermis becomes thickened and edematous and produces elongated rete cones of irregular shape.

ACNE VULGARIS. This is the well-known cross that almost every adolescent has to bear—the common and disfiguring pimple. It consists of an oversecretion of sebum and is, therefore, associated with "greasy skin." The ducts of sebaceous glands become clogged with secretion, the outer layer of which, being blackened by adhering dirt, is then known as a "blackhead" or comedo. Secondary invaders complicate the picture

by causing local infection within the sebaceous ducts and in their supporting tissue, and this produces tiny localized abscesses which constitute the red pimple. Microscopically it may be noted that the abscesses in the follicles remain superficial and do not penetrate to the corium like boils or carbuncles. Discharge of a droplet of pus or the drying up of the small abscess by resorption terminates the process.

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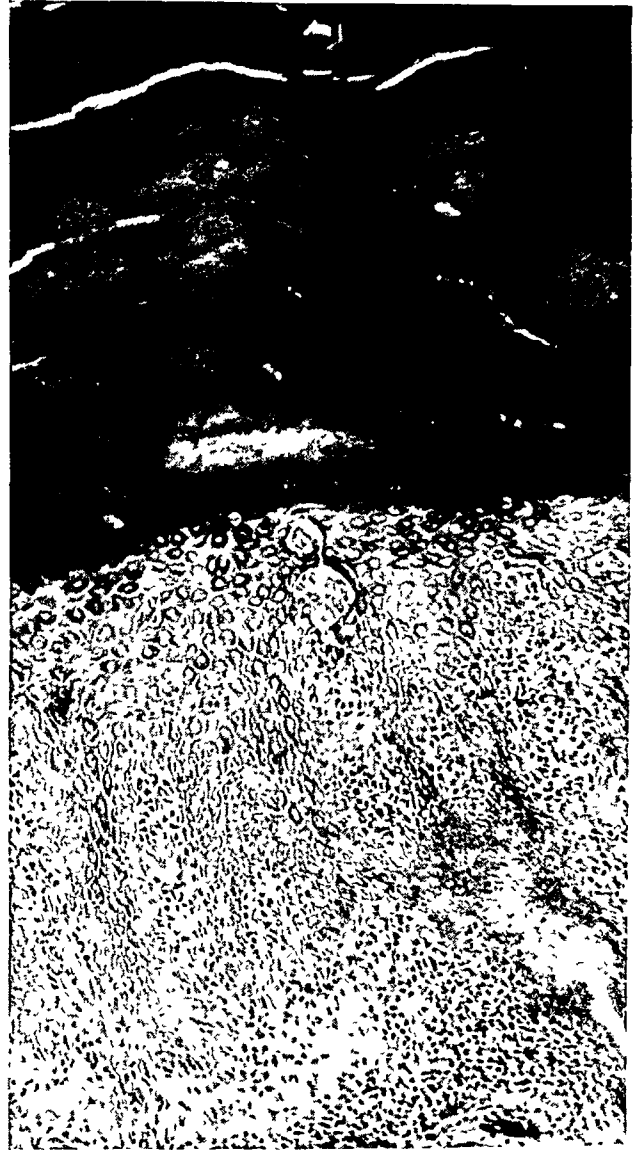
papillae which sometimes extend into it until their apices lie just beneath the scaly layer. This accounts for the tiny bleeding points just mentioned. The rete malpighi is swollen and pale, the epidermis is edematous, and clear spaces (called "air-spaces") surround the nuclei of its prickle cells. As the process continues, the stratum granulosum disappears. The scaly outer layer



Lesion of chronic psoriasis. Note hyperkeratosis (which veils parakeratosis in this case), long rete cones, and penetration of rete by papillae almost to horny layer. "Air spaces" are visible as small white vacuoles in rete. Slight perivascular lymphocytic infiltration is visible in corium.

shows true air spaces, which account for its silvery appearance on gross examination. Polymorphonuclear leukocytes may invade the epidermis in pronounced cases. In very chronic lesions the horny layer becomes broken up into papillary masses of combined hyperkeratosis and parakeratosis; this is known as the "verruccose stage." There is a pustular type of the disease in which the surface of the lesion becomes encrusted with exudate that lies between the horny layer (which is lifted off by the masses of leukocytes) and the underlying strata of cells. The nails and the mucosa of the oral cavity may also be affected. The important lesions, then, are: parakeratosis, acanthosis, edema and small abscesses in the epidermis, ab-

sence of the stratum granulosum, marked dilatation of the papillary vessels with penetration of the epidermis by the papillae, relatively little change in the corium, and



Section of skin from patient with longstanding chronic psoriasis. Note tremendous hyperkeratosis resembling that of a clavus. Cells of rete are pale, and papillae penetrate epidermis almost to keratinized layer. Parakeratosis is masked by dense orange stain of keratinized cells.

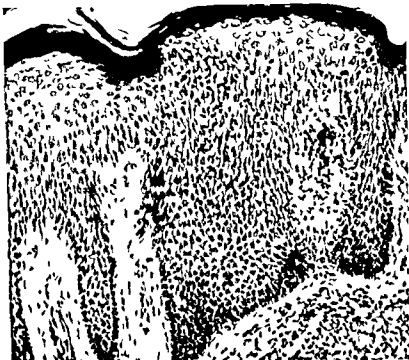
an exudate that is characterized by the absence of plasma cells.

PARAPSORIASIS. Only two types of this will be considered here, both known by French names: "parapsoriasis en gouttes" and "parapsoriasis en plaques." The Germans call these respectively "pityriasis lich-

inoides chronica" and "erythroderma maculosa chronica"

Parapsoriasis en Gouttes In this there are widespread yellow or salmon colored macules and papules covered by small whitish and firmly attached scales. These scales unlike those of psoriasis, are scraped off with some difficulty and leave no bleeding

counts for the lack of bleeding points under the scales. The vessels of the corium show moderate sleeves of lymphocytes, and an occasional polymorphonuclear may be seen. As the lesion heals there is loss of prickly cells and the stratum spinosum becomes narrowed. Obviously one must know something about the macroscopic appearance of



Lesion of parapsoriasis "en gouttes" Parakeratosis is well demonstrated in horny layer at upper left. Rete is invaded by lymphocytes, and there is a diffuse infiltration of these cells into the corium. The rete cones are very asymmetrical.

points behind. Seen microscopically there is moderate hyper- and parakeratosis, more marked toward the center of the lesion. The stratum granulosum is lacking beneath the areas of parakeratosis and underdeveloped throughout the lesion. There is some edema of the epidermis, and a few leukocytes may be found wandering among the cells. The basal cells may become dissociated, stain poorly, and be unrecognizable. The papillae are widened and do not penetrate the epidermis, although they may thin it out considerably. Up to this point the similarity to psoriasis has been marked, here we have a divergent sign which ac-

counts for the lack of bleeding points under the scales. The vessels of the corium show moderate sleeves of lymphocytes, and an occasional polymorphonuclear may be seen. As the lesion heals there is loss of prickly cells and the stratum spinosum becomes narrowed. Obviously one must know something about the macroscopic appearance of

the lesions in a given case to be able to diagnose this with any certainty. *Parapsoriasis en Plaques* This differs from the preceding form in having sharply limited shield like plaques that are either smooth and pale yellowish or very red and covered with fine scales. They occur chiefly on the buttocks and extremities and are not infiltrated. They are unsightly rather than troublesome, as they cause no symptoms.

There are a number of dissimilarities between the microscopic picture in this and in the preceding variety. There is slight acanthosis, and the rete cones are atrophic and may disappear, leaving a very thin epi-

dermis to cover the lesion. The stratum corneum is loosely attached and may show slight overgrowth, but parakeratosis is rare or very sketchily developed. The stratum granulosum is poorly developed and may be lacking here and there. As in the other type, there are alterations in the basal layer of cells that render them unrecognizable. A few wandering leukocytes may be found in the epidermis. There is a scanty and diffuse infiltration of lymphocytes in the widened papillae. Fairly thick sleeves of these cells ensheath the vessels of the subpapillary layer of the corium.

PITYRIASIS ROSEA. This is characterized by flat red papules of miliary size which appear in groups that constitute oval or rounded plaques 1 to 3 cm. in diameter. These have a raised border that is reddish, and the center of the lesion is covered with yellow to brownish scales. A small "herald spot" usually develops a week or so before the eruption becomes general. The microscopic appearance of the lesion is much more dramatic than its gross appearance would indicate. Microscopic vesicles form beneath the horny layer, and these are later replaced by areas of parakeratosis. The papillary and subpapillary layers of the corium show well-marked signs of inflammation. The epidermis is edematous, and there are numerous lymphocytes within the intercellular spaces, sometimes forming small clusters in a vacuole caused by the dissolution of the epithelium. There may be definite acanthosis. The papillae become much swollen, and the vessels of the corium are surrounded by infiltrates of lymphocytes and leukocytes. There may be a slight increase in the collagenous tissue of the pars papillaris.

LICHEN RUBER. Lichen ruber is another laboratory staple, many biopsies showing this lesion. There are three types of the disease: lichen planus, lichen planus acuminatus, and lichen planus verrucosus; as these are clinical stages in the same disease, separation into these groups is not particularly important to us. The type known as planus

produces flat papules scattered widely over the skin; that known as acuminatus shows a predilection for the follicles of the sebaceous glands and hairs.

The microscopic picture is so typical that one is apt to speak of "lichenoid lesions" that resemble this prototype. One finds a gently bulging lesion on section, over which



Early lesion in lichen ruber planus. There is a subepidermal zone of diffuse lymphocytic infiltration and invasion of the rete by lymphocytes. Stratum granulosum is thick and prominent.

there is a corn-like hyperkeratosis, almost invariably without parakeratosis. The stratum granulosum is thickened, and the number and size of the granules of keratohyalin are greater than normal. The malpighian layer is the site of acanthosis, and the rete cones vary in size and shape. Where the inflammation is most intense these may be lost entirely or remain as thinned-out, narrow, feathery cords of cells. The elements of the stratum spinosum show resistance to stains and become homogeneous; they tend

to fuse with one another. There is marked nuclear degeneration and destruction. The basal cells become separated by edema and by lymphocytic infiltration, so that this layer acquires a frayed out and indefinite appearance.

The changes in the papillary layer of the corium are probably the most striking and characteristic part of the lesion. There is a wide, diffuse band of dense lymphocytic exudate beneath the basal layer of the epidermis and penetrating it at points. No plasma cells are found here. An occasional polymorphonuclear may be found straying near a vessel. With this infiltration there is a destruction of elastic tissue and hyaline degeneration of the collagenous fibers until they, too, may be destroyed. As the disease progresses one notes a sinking of the center of the lesion and the formation of a flat, atrophic epidermis without rete cones. There is a form of this disease that begins with atrophic changes that progress rapidly; the atrophic epidermis overlying a button like infiltration of lymphocytes.

ROSACEA (ACNE ROSACEA) The familiar "toddly blossom" or thickened red nose of the chronic toper is an example of this condition which, unfortunately for the patient, is not always attributable to the ingestion of alcohol and may mar the features of models of sobriety. At first there is a hyperemia of the nose and the face adjoining it, but acne like pustules develop later. The vessels of the skin are passively congested, and a thickening of its connective tissue may go over into a nodular, keloid hypertrophy which coarsens the epidermis, results in gaping pores, and converts the nose into the unsightly structure made famous by Rembrandt. This is "rhinophyma." The operation for this consists in the literal whittling off of strips of the thickened integument, and these are sometimes submitted for examination in the laboratory.

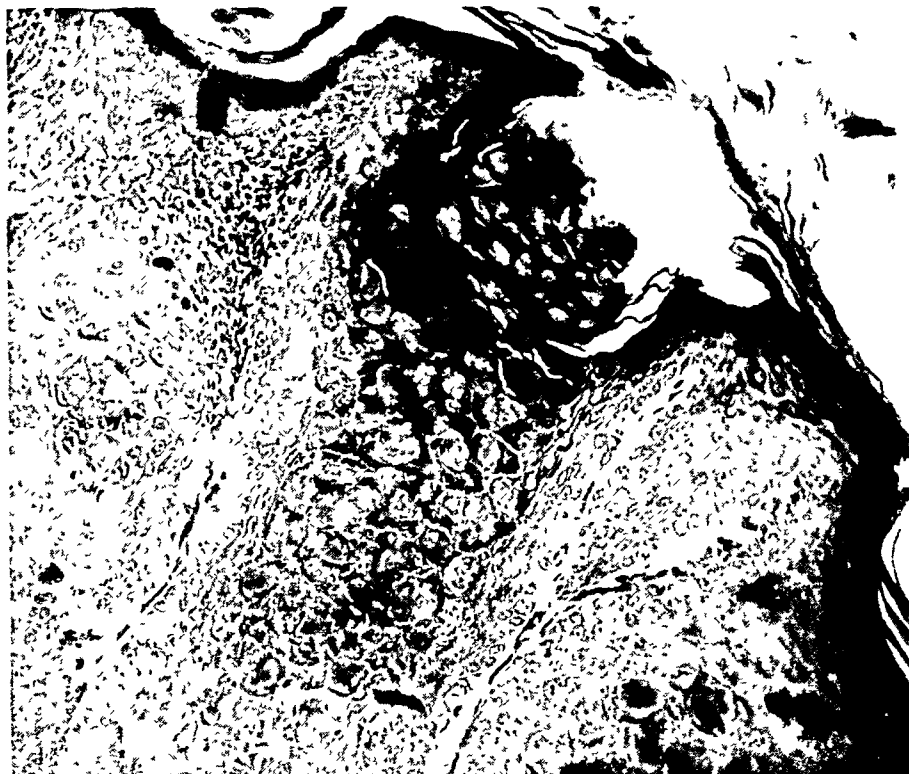
The microscopic lesion consists of a simple dilatation of the capillaries, which may be surrounded by the equivocal lymphocytic exudate, by now all too familiar to

the reader. The elastic tissue degenerates, and the hyperplasia of the collagenous fibers leads to a condition similar to that seen elsewhere in elephantiasis. As the disease progresses, the infiltrate becomes almost tubercular, with epithelioid and even giant cells present and polymorphonuclear leukocytes added to the picture. Abscesses form and discharge onto the surface, to be replaced by cicatrices.

(RHINOPHYMA) Further progression of the lesion into the stage of rhinophyma results in the hyperplasia of the sebaceous glands, the entire section becomes studded with them. The follicles become dilated into small sacs containing a good deal of horny material and sebum. Another form of rhinophyma is the angiectatic, in which the epidermis undergoes atrophy and there is an overgrowth of dense fibrous tissue rich in dilated vessels and capillaries.

Chronic Specific Inflammations. MOLLUSCUM CONTAGIOSUM This is definitely a viral infection that leads to foci of hypertrophy of the epidermis and the formation of molluscoid little growths with umbilicated or saucer like craters. These are often mistaken for warts or moles. One may sometimes discern small cystic areas in the epidermis, but usually the lesion is not very readily recognized on gross examination by the uninitiated. In sections, however, it has a microscopic appearance so typical that, once seen, it is never forgotten. There is hyperplasia of the cells of the rete malpighi in which small acidophile and ovoid inclusion bodies form and grow until they are as large as normal epithelial cells. There is great proliferation of rete cones and consequent narrowing of the dermal papillae, but the lesion is well limited to the epidermis and most marked in the region of the granular layer where the inclusion bodies have matured and are large and unmistakable. There is little or no inflammatory reaction to their presence.

TUBERCULOSIS As has often been said in this book, tuberculosis is tuberculosis wherever one meets it, the lesions may differ in



Typical lesion of molluscum contagiosum, showing cup-like retraction on surface and intracellular inclusion bodies.



Lesion of molluscum contagiosum developing at center of a dermal papilloma in which there was also a nonmalignant melanoma (not shown here). Note dark inclusion bodies in epithelial cells. Two masses of these at center of field are densely keratinized.

some respects, veering toward caseation at one end of the scale and toward fibrosis and diffuseness at the other, but somewhere in the specimen the classic features of the tubercle can usually be found. Giant cells and epithelioid cells in circumscribed masses, or tubercles, will usually make the diagnosis certain, the demonstration of the micro bacillus of tuberculosis is not often easy

pressed elsewhere in this book. The writer takes particular exception to including Hodgkin's disease under possible tuberculous infection, and the modern conceptions concerning lupus erythematosus do not indicate that it should be placed in this group. Boeck's sarcoid is still believed by some eminent pathologists to be a form of tuberculosis, while others disagree with that as



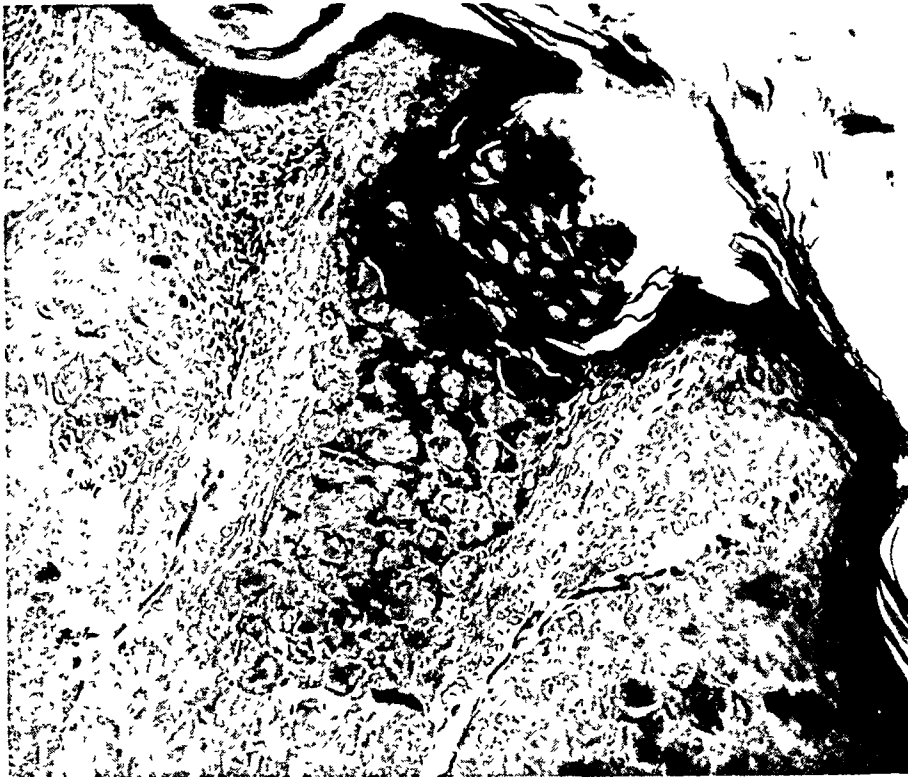
Section of skin from lesion of lupus vulgaris. Note widespread and obliterative tuberculous infiltration of corium. The epidermis has been much thinned out.

McCarthy divides the dermal lesions into a number of groups. The first represents localized and progressive lesions and includes lupus vulgaris, verrucose tuberculosis, scrofuloderma, and ulcerative forms. The second includes miliary tuberculosis, lichen scrofulosorum, papulonecrotic tuberculi, tuberculosis indurativa, Boeck's miliary lupoid (sarcoid), and angiolupoid. In the third group he arrays a number of "diseases of somewhat doubtful tuberculous origin," such as lupus erythematosus, lichen nitidus, granuloma annulare, exfoliating erythrodermatitis, Hodgkin's disease, and the chilblain lupus of Hutchinson.

One may see at a glance that a number of these do not agree with the opinions ex-

sumption. Lupus pernio and lichen nitidus might be considered variants of Boeck's sarcoid. It would be unprofitable to go into the niceties of all these subdivisions of dermal tuberculosis, and a brief outline of their characteristics should suffice.

Lupus Vulgaris Lupus vulgaris begins as a soft little papule the size of a pinhead, and when seen pressed under a glass it looks like a small globule of apple jelly. Other papules appear and fuse, while the lesion begins to heal at its center. New papules continue to develop at its periphery and are occasionally scaly. This may go on until the lesion begins to simulate that of psoriasis. This form is known as the "flat type." An elevated, hypertrophic variety



Typical lesion of molluscum contagiosum, showing cup-like retraction on surface and intracellular inclusion bodies.



Lesion of molluscum contagiosum developing at center of a dermal papilloma in which there was also a nonmalignant melanoma (not shown here). Note dark inclusion bodies in epithelial cells. Two masses of these at center of field are densely keratinized.

some respects, veering toward caseation at one end of the scale and toward fibrosis and diffuseness at the other, but somewhere in the specimen the classic features of the tubercle can usually be found. Giant cells and epithelioid cells in circumscribed masses, or tubercles, will usually make the diagnosis certain, the demonstration of the microbacillus of tuberculosis is not often easy

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may be observed on the ears and nose; this tends to ulcerate, leaving denuded and unclean craters. With this there is a good deal of healing and fibrosis which leads to distortion of the face, with grotesque contractures and the production of shining, red, and radiating scars that pull the features awry. Small yellowish-white miliary tubercles may occur concomitantly upon the mucosal surfaces of the nares.

The histology of lupus is similar to that of tuberculosis in general, but its tubercles are characterized by being composed almost exclusively of epithelioid cells with few or no giant cells, while caseation is very uncommon. The epidermis may remain little affected, or exhibit acanthosis. The sub-varieties of lupus show a number of somewhat differing lesions. In the miliary, acute and disseminated form the lesion appears as collections of "apple-jelly" papules from the size of a pinhead to that of a small pea (2 to 4 mm. in diameter). They do not coalesce, but tend to heal and regress.

Lupus pernio is so similar to Boeck's sarcoid that it is now considered by many to be the same lesion. In the verrucose form of lupus the epithelium is thrown up into numerous warty structures, the epidermis being affected in such a way as to cause hypertrophy and hyperkeratosis, instead of remaining practically normal, as in ordinary lupus. Scrofuloderma is a nodular invasion of the skin by tuberculous tissue from an underlying lesion such as a tuberculous lymph node.

Eruptive Types. In rare cases miliary tuberculosis invades the skin in its typical form, involving the integument of the trunk and extremities with innumerable tiny tubercles. In lichen scrofulosorum there may be a somewhat similar lesion, but the pinhead tubercles tend to be aggregated into round or oval patches. Under the microscope one finds transitions from collections of lymphocytes to typical specific tubercles. This may cause confusion with syphilitic lesions. The infiltrate in this form always

maintains a focal character and does not tend to diffuseness as in lupus.

Papulonecrotic Tuberculids. In dermatology it is customary to use the termination "-id" to indicate that a lesion is an indirect manifestation of a given infection, such as an allergic phenomenon. Thus the "tuberculids" occur in connection with a tuberculous infection, the "trichophytids" with trichophytous infections of the feet (appearing elsewhere as an eruption), and so on.

There are subtypes of the tuberculids. One of these, folliclis, is very superficial and is found within or about follicles. Small papules a few millimeters in diameter form in the superficial layers of the corium and assume a dark brown color. Pustular necrosis occurs at their centers, and the resulting plug is discharged through the epidermis, leaving behind it a small ulcer with punched-out margins. In the variety known as "acnetis" cherry-sized masses grow in the subcutaneous tissue of the face and hands and work their way through cutis and epidermis to produce lesions similar to those of folliclis, but larger. A third acneform type exhibits softer papules that tend to become pustular; these may accompany lichen scrofulosorum. Here the lesions at first reveal a very strange necrosis and disintegration of the corium without much involvement of the epidermis. This may be followed by a reaction of polymorphonuclear leukocytes, while still later typical tuberculous tissue finally puts in an appearance.

While tuberculids are in the nature of allergic reactions to the toxins of the tubercle bacilli, these have been isolated from them and injections into guinea pigs have resulted in infection. Vascular lesions are more marked in the tuberculids than in the more definitely infective tuberculous group.

Erythema Induratum. This is a dermal infection presenting few distinctive clinical signs, and *M. tuberculosis* should not be considered as a factor unless there are signs of tuberculosis elsewhere in the patient. The lesion may be closely imitated by syphilis,

leprosy, and other infections that produce fibrosis and induration

Histologically it is a deep seated lesion of the adipose panniculus where large tubercles are produced, these are almost exclusively composed of epithelioid cells, giant cells and lymphocytes being variable in numbers. In the later stages of the disease the tubercles invade the pars papillaris and fuse into a subepidermal layer of tuberculous granulation tissue. Darier's sarcoid resembles this lesion closely, the Darier-Roussy type is less definitely tuberculous. In any case the lesions remind one of those of panniculitis or multiple fat necroses.

BOECK'S SARCOID OR VILIARY LUPOID We have considered elsewhere the tubercle of this disease (granulomas). McCarthy prefers the designation "lupoid" to "sarcoid" when referring to the dermal lesion of the disease. This resembles lupus on account of its tubercles, which may or may not contain giant cells and are composed chiefly of epithelioid cells. These lie in the corium just beneath the epidermis and are sharply defined, they contain a few fibroblasts and lymphocytes in addition to their epithelioid elements, but fail to caseate. Kyrle demonstrated acid fast bacilli in the lesions, but these organisms were not typical tubercle bacilli. Patients usually give a strongly positive von Pirquet reaction, although the Mantoux test is negative. The differences between this dermal lesion and those of lupus pernio and lichen nitidus are highly technical. The former are more deeply seated than those of Boeck's lupoid and tend to have their long axes parallel with and not at right angles to the epidermis. Lichen nitidus presents a looser architecture, more lymphocytes, and more giant cells than does Boeck's lesion.

LUPUS ERYTHEMATOSUS We know today that this is a systemic disease connected with vascular lesions that are characterized by fibrinoid degeneration of the adventitia. There may be acute exacerbations of the disease with widespread lesions on the body, but it is usually confined to the exposed por-

tions and is very unfavorably affected by sunlight, which seems to increase its severity. The typical dermal lesion is a "butterfly" over the nose and cheeks that is superficially similar to that of lupus vulgaris, whence its name. A small, ovoid, reddish,



Dermal lesion of lupus erythematosus disseminatus in corium beneath an atrophic and not otherwise very much altered epidermis. There are large masses of serpiginous perivascular exudate composed of lymphocytes.

elevated lesion appears on the face and spreads. Its borders are erythematous, exhibiting dilated vessels, while its center is atrophic and sunken and covered with small whitish scales that adhere firmly to it.

The histologic picture is very atypical and centers about the corium rather than the epidermis. The vessels are dilated and exhibit lymphocytic sheaths, later the exudate is not exclusively perivascular, but spreads in the form of fusing clumps through the corium. Both elastic and collagenous

may be observed on the ears and nose; this tends to ulcerate, leaving denuded and unclean craters. With this there is a good deal of healing and fibrosis which leads to distortion of the face, with grotesque contractures and the production of shining, red, and radiating scars that pull the features awry. Small yellowish-white miliary tubercles may occur concomitantly upon the mucosal surfaces of the nares.

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histologic features are very typical, being characterized by the "leprosy cell," globi of Neisser, and a diffuse granulomatous tissue fairly swarming with acid fast bacilli which cause astonishingly little inflammatory reaction about the lesion. This centers in the corium, where there is a broad band of granulation tissue composed of collagenous fibers and pale epithelioid cells containing bundles or masses of bacilli. A few lymphocytes and plasma cells are also present, and there are large pale cells presenting vacuoles that may almost replace the entire cytoplasm and that contain decomposed masses of bacilli. These are the "Virchow cells." The description might be simplified by stating that the foamy epithelioid cells and the Virchow cells are merely phases of the familiar phagocyte. Cowdrey divides the bacterial clumps into "globi," subdivisible into "cigar bundles," and "seed globi," and distinguishes "giant globi," which are the masses in the large, vacuolated Virchow cells. Cigar bundles are masses of bacilli arranged parallel so that they resemble



Section from one of the tubercular lesions of leprosy patient shown on page 466. Note vacuolated cells in dense zone beneath characteristically fibrotic pars papillaris. Epidermis is little altered (Col F H Foucar)



Oil immersion photomicrograph of bacilli of leprosy in lesion of patient whose photographs are shown elsewhere. Ziehl-Neelsen stain was used (Col F H Foucar)

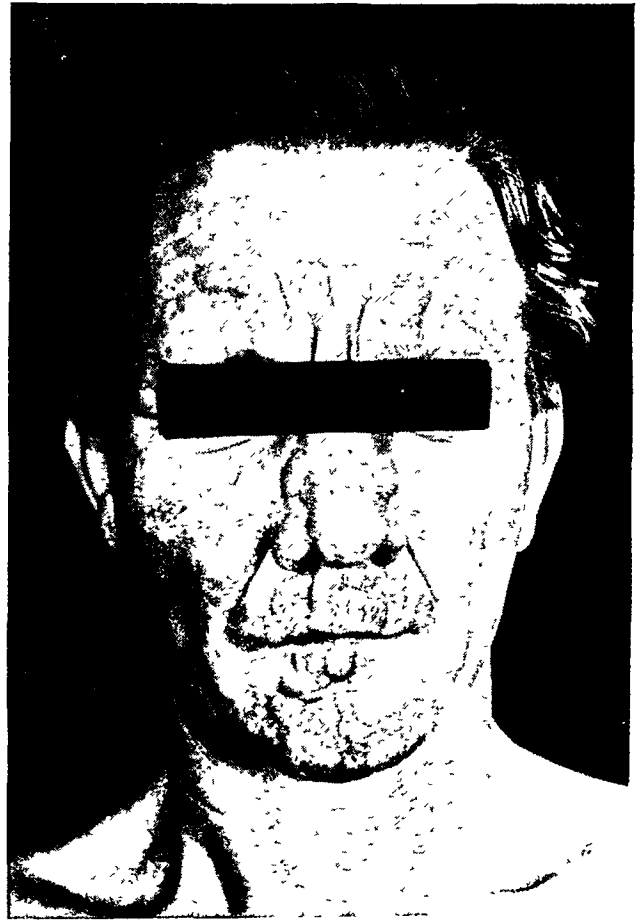
fibers degenerate and may be destroyed. McCarthy states that changes in the vascular walls are practically absent; this is paradoxical in view of the walls' appearance in the renal, splenic, and other arterioles, but it is borne out by our experience with the dermal lesions.

As the disease progresses the epidermis suffers; hyperkeratosis develops and follows the wavy outline of the surface, dipping into the follicles. The stratum granulosum is generally well maintained, but where it is lacking there will be an area of parakeratosis just over its former site. The malpighian layer is edematous, and it loosens, loses its rete cones, and atrophies. The intercellular bridges disappear, and the basal layer becomes depigmented. There is no pustulation or necrosis; rather the skin becomes scarred by hyperplastic fibrous tissue.

DERMAL SYPHILIS. It has well been said that syphilis is a protean disease. For a description of its numerous and varied dermal lesions the reader is referred to textbooks on dermal pathology or syphilis rather than to this limited volume. It would be well to remember that any lesion exhibiting extensive vascular proliferation, frank angitis, or perivascular grouping should be suspected of being of luetic origin. This disease may then be ruled out or its presence confirmed by reference to the clinical data in the case and a process of exclusion. The reacting cell in syphilis is the lymphocyte, which unfortunately constitutes the chief element of many perivascular lesions in dermatologic pathology. Thus it is of little value in assisting one to a diagnosis. The lesions in dermal syphilis may be papillary, raised papillary, papulosquamous, pustular, ulcerated, or of a type known as "lues maligna" that produces changes resembling early malignant transformation. There are also vegetating lesions, such as the condyloma latum or "flat condyloma" of the vulva. Diffuse miliary lesions and others resembling erythema nodosum may be noted. In the tertiary stage gummata may be found in the skin, or there may be ulcerative tuber-

cular lesions known as "syphilids." This will give some idea of the scope of the subject and convince the reader that there is something in the old saying "when in doubt, diagnose syphilis."

LEPROSY. Leprosy is a chronic inflammatory disease that develops very insidiously,

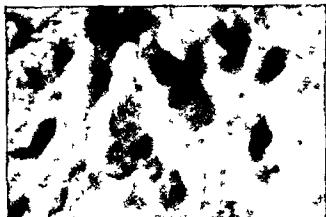


A leper of American stock. Note tubercular wheals over the lips and chin and thickened folds of skin above eyes and over bridge of nose. This distribution produces "leonine facies." (Col. F. H. Foucar.)

having probably one of the longest incubation periods of any infection. It produces granulomata in the skin. Two forms of the disease are recognized: the tubercular or nodular and the maculo-anesthetic.

Tubercular or Nodular Form. This causes brownish-red papules or nodules anywhere on the surface of the body, particularly on the face and the extensor aspects of the limbs. The lesions may remain discrete or may fuse to form lobulated and disfiguring masses that are furrowed and thick. The

PLATE XI



High powered Kodachrome photomicrograph of organisms in lesion of leprosy shown elsewhere. Note beginning globoid body at center and the scattered bundles and single bacilli. Ziehl-Neelsen stain was used. (Col. I. H. Fowler)

bundles of cigars; seed globi are a rather run-together and degenerate form of these, and the giant globi represent these plus a mucoid material which is not mucus (or "Schleim" as it was described by the Germans) and which Cowdrey calls "schleim." His reason for doing so is not clear. (See color plate.)



Back of leprosy patient whose face is depicted on p. 466. White and patchy type of anesthetic lesion is well shown here. (Col. F. H. Foucar.)

The nodules of such infiltrates as that just described are separated by coarse bands of connective tissue. Giant cells are occasionally present and may exhibit asteroid bodies. There is a subtype of lesion, the "tuberculoïd form," in which the histology simulates that of lupus vulgaris. There are tubercles composed of a core of epithelioid cells and giant cells, surrounded by lymphocytes. Unlike the more usual type, this one reveals very few bacilli in the sections.

Maculo-anesthetic Variety. In this type of leprosy the histologic lesion is quite unique, as it gives morphologic evidence

of involvement of nervous trunks and endings by hordes of bacilli without producing any other very specific lesion in the surrounding tissue. A chronic inflammatory exudate is found around the vessels, later becoming diffuse and interfering with the nourishment of the epidermis, which exhibits some hyperkeratosis and slight changes such as the formation of vesicles.

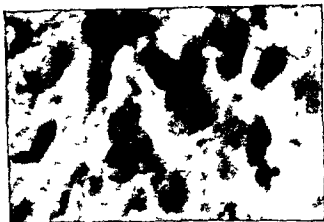
ORIENTAL BOIL (ALEPPO BOIL, BISKI BUTTON, DELHI SORE). While the flagellate *Leishmania donovani* may cause generalized disease in the case of kala-azar, it also causes button-like lesions in the skin which may break down and form ulcers in some instances. The Mediterranean strain of *Leishmania* is the factor in the button-like lesion while certain South American strains bring about tropical ulcers. The Oriental boil begins as a red and itching papule on exposed portions of the body, looking not unlike an insect bite. It enlarges until it forms a nodule that is hard and infiltrated and measures several millimeters to a centimeter in diameter. Around it is a zone of inflamed skin.

The parasite, which grows on culture media as a flagellate organism of fusiform outline with tapering extremities and anteriorly situated flagellum, is never seen in this form in human tissue, where it is small, spherical-to-ovoid body exhibiting two nuclei. One of these, the trophonucleus, is transversely directed; the other, the kinetonucleus, is punctate. The kinetonucleus is a sort of blepharoplast which is associated with the flagellum.

Microscopically the lesion is granulomatous, and the parasites are found chiefly near the ulcerated epidermis. The chief reacting cell is the macrophage, and in one of these there may be included several of the parasites. These phagocytes are seen wandering through the layers of the epidermis near the ulcer. As the lesion matures it becomes tubercular in appearance and the parasites are more difficult to find.

RHINOSCLEROMA. A disease of the nose and upper lip, this lesion begins in the

PLATE VI



High powered Kodachrome photomicrograph of organisms in lesion of leprosy shown elsewhere. Note beginning globoid body at center and the scattered bundles and single bacilli. Ziehl Neelsen stain was used (Col F H Foucar)

mucosa of the nares and extends out to the surrounding skin in the form of bluish red bands of tissue forming nodes or plaques that may become cartilaginous in consistence and even interfere with breathing. It is caused by an encapsulated bacillus (the bacillus of rhinoscleroma) which resembles the Friedländer bacillus and may belong to the same family. The histologic picture is characterized by the presence of large numbers of foam cells (macrophages, as usual), known here as "rhinoscleroma" or "Mikulicz" cells, which contain the organisms. Numbers of plasma cells are also present, as a result of which there are also abundant Russell bodies. The epidermis is not much affected, the cutis being filled with granulomatous masses of these cells and bearing the brunt of the infection. There has been considerable dispute as to the origin of the Mikulicz cells, but there seems little reason to consider them anything but phagocytes which, in so many other lesions, may take on this foamy appearance. That the Russell bodies should be mentioned as typical of rhinoscleroma probably stems from the fact that few dermatologic lesions are so rich in plasma cells. These bodies may be seen anywhere that plasma cells are found in quantities, even in gastric ulcers. The outcome of rhinoscleroma is the production of a keloid fibrosis with hyaline degeneration of the bundles of collagen.

Dermatomycoses The group of diseases known as dermatomycoses are attributable to infection by fungi and yeasts, on the whole they are relatively rarely seen in the laboratory of pathology, and for this reason some of the commoner forms will be reviewed.

BLASTOMYCOSIS This is divisible into the North American type (which has two subgroups, blastomycosis and coccidioidal granuloma), the European type, and the South American type of Escomel.

NORTH AMERICAN TYPE *Blastomycosis* This may occur anywhere and is fairly common in North America. It is a superficial disease, beginning as painful nodules that

become abscesses, break out to the surface, and extend. Large ulcerated foci, like untidy plaques that resemble verrucous tuberculosis, develop and usually spare the regional lymph nodes. The microscope reveals small abscesses in swollen and proliferated rete cones which tend to wall off islands of the cutis in their anastomatic meshes. Here granulation tissue is formed. The inflammation is subacute and exhibits many plasma cells and occasional giant cells, with some abundance of epithelioid cells. A search with the low powered objective may reveal within a few of the giant cells the doubly contoured globoid bodies that are the parasites. On culture media they assume a mycelial form, not observed when they are in human tissue. They measure from 10 to 18 μ and are refractile, with a double contour that gives the effect of one hollow sphere containing another slightly smaller sphere with a space between the two "shells." The organism, like the yeasts, multiplies by budding.

Coccidioidal Granuloma California and the southwestern United States are the most likely regions for this form of blastomycete; it differs from the preceding one in having a generalized distribution instead of forming a primary lesion and remaining localized in the skin. It may cause lesions that are much like tuberculosis in their appearance in the internal organs, notably the lungs. The suprarenals are also affected. The microscopic appearance is that of an infectious granuloma resembling tuberculosis. The demonstration of the organism (*Coccidioides immitis*) is the diagnostic feature. It varies from 5 to 30 μ in diameter, having a far wider variation in size than blastomycetes, like that organism it has a double contour, but it multiplies by means of endospores and not by budding, which is another differentiating feature. The endospores may be stained with ordinary aniline dyes.

EUROPEAN TYPE This rather rare disease, attributable to infection by a saccharomycete or yeast, was first described by Busse and Buschke. There are nodules on the skin

sions usually represent mixed infection. The primary lesion is lichenoid in its appearance. Similar infections (dyshidrosis) may be caused by one of several families of *Ept dermatophyton*, which is closely allied to *Trichophyton*.

DERMAL MANIFESTATIONS IN LEUKEMOID DISEASES The skin may be the site of small,

liminary stages preceding it ("mycosis fungoides d'emblee"). Internal organs are involved only in exceptional cases. The blood shows an eosinophilia that varies from 3 to 35 per cent. Biopsies are of little value in the first stage, which resembles psoriasis, form eczema, one can tell much more by looking at the patient.

The disease occurs between the 40th and 60th years of age. It consists of a stubborn eczematoid dermatitis that may persist for years; this is followed by the development of papules and nodules that correspond to



Area of dermal infiltration in leukemia. Epidermis is little involved, but there is dense infiltration of dermal papillae by leukemic elements, in this case lymphocytic in type.



Lesion of mycosis fungoides, showing invasion of epidermis by lymphocytic elements that are also forming quasi-neoplastic complexes about vessels of corium. Many of the cells are large and atypical and exhibit mitotic figures which cannot be made out at this magnification.

miliary foci of lymphoid or myelogenous leukemia, of Hodgkin's disease, and (according to Pollitzer) of reticulo endotheliosis. These lesions have been described in the appropriate section.

MYCOSIS FUNGOIDES McCarthy divides this sharply from the manifestations just mentioned, believing that the disease is primary in the skin and unconnected with leukemia. Three stages are recognized: the eczematoid, the infiltrative, and the neoplastic. There may, however, be a sudden development of the last of these without the pre-

the second stage. The lesions are of variable size, irregularly outlined with raised, reddened and serpiginous borders that may be interrupted by fairly normal skin at one point, so that they form incomplete circles. They tend to fuse in time. In these geo-

which ulcerate. Microscopically they are seen to have necrotic centers surrounded by leukocytes, epithelioid cells, lymphocytes, and giant cells which contain the yeasts. These may be found in large numbers in the purulent centers of the lesions. There is remarkably little pathologic alteration in the skin other than that in the immediate vicinity of the ulcers.

SOUTH AMERICAN TYPE (of Escamel). This must be differentiated from tropical ulcers, bouba, and espundia, all of which are caused by *Leishmaniae*. In this case the parasite is an endomycete that causes tubercular nodules in the cutis and subcutis, the centers of which contain abscess-like cavities walled off by epithelioid cells and containing large numbers of the parasites.

SPOROTRICHOSIS. Skin infected with *Sporothrix* exhibits widely scattered solid or fluctuant nodules that are surrounded by a violaceous halo and resemble tubercular syphilitic lesions. They lie in the cutis or subcutis, may be scattered at random over the surface, or may follow lymphatic channels. There is also a hypertrophic or verrucous form. From the histologic standpoint the lesion is an infectious granuloma in which the *Sporothrix* should be identified by cultural methods and animal inoculation. It resembles that of lymphogranuloma venereum in that it shows an outer lymphocytic zone, a median zone of epithelioid cells, and a central area of necrosis and pus.

TRICHOPHYTOSIS. The *Trichophyta* cause a very superficial infestation (familiarily known as "ringworm") by their mycelial growth which produces oval areas of inflammation that are slightly infiltrated and covered with scales, vesicles, or pustules. The center of the lesion heals as the peripheral portion spreads away from it. Biopsies are unnecessary, as the fungus may readily be demonstrated by scraping off a few scales, soaking them for half an hour in 30 per cent KOH, gently heating this over a burner, and then staining the slide with polychrome methylene blue, which demonstrates the mycelium. A deeper form of the lesion may

enter the follicles and produce folliculitis and perifolliculitis, by reason of which boggy, nodular lesions develop. This form is known as "kerion celsi" when seen upon the scalp, as "sycosis parasitaria" when on the bearded skin. Here the diagnosis is made by epilation and examining the roots of the hairs, which will be found to be invaded by the fungus. The deeper lesions are granulomata and contain epithelioid and giant cells. Somewhat similar lesions are produced by *Trichophyton violaceum*. The organisms in this may be readily cultivated by dropping an infected hair into broth and incubating it, whereupon a copious growth of moniliform chains will be obtained. Interposed among the trichophyta are larger, more refractile forms that represent the spores.

On the feet, the familiar ailment "athlete's foot" is usually produced by one of two *Trichophyta*: most commonly the *gypseae*, less often the *purpurea*. The former grows on slants as a fuzzy white colony that resembles cotton batting, the latter less luxuriantly and with a purplish hue. These produce small vesicles on the skin that are scaly and result in the production of "soft corns" between the toes or on the soles. The organism is readily detected by scraping off scales and examining them after maceration with lye. Biopsies are unsatisfactory, as there is always difficulty in demonstrating the very superficial growth of fungi in stained sections. Toenails affected with this disease become crumbling, opaque, and white, and ultimately they are destroyed. Secondary infection is common, and therefore before operations are performed on the feet the disease should always be looked for and treated in order to guard against introducing the secondary invaders into the deeper tissue. Vesicular, yellowish-brown eruptions (trichophytids) may arise on the inner surface of the thighs or other moist localities as a result of allergy to the fungus. These are superficial and itch intensely. The microscopic picture of the infection is unilluminating, as it is very superficial; deeper le-

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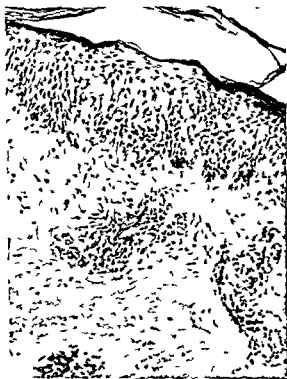
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The disease occurs between the 40th and 60th years of age. It consists of a stubborn eczematoid dermatitis that may persist for years; this is followed by the development of papules and nodules that correspond to



Area of dermal infiltration in leukemia. Epidermis is little involved, but there is dense infiltration of dermal papillae by leukemic elements, in this case lymphocytic in type.



Lesion of mycosis fungoides, showing invasion of epidermis by lymphocytic elements that are also forming quasi-neoplastic complexes about vessels of corium. Many of the cells are large and atypical and exhibit mitotic figures which cannot be made out at this magnification.

miliary foci of lymphoid or myelogenous leukemia, of Hodgkin's disease, and (according to Pollitzer) of reticulo endotheliosis. These lesions have been described in the appropriate section.

MYCOSIS FUNGOIDES McCarthy divides this sharply from the manifestations just mentioned, believing that the disease is primary in the skin and unconnected with leukemia. Three stages are recognized: the eczematoid, the infiltrative, and the neoplastic. There may, however, be a sudden development of the last of these without the pre-

ceding stages. The lesions are of variable size, irregularly outlined with raised, reddened and serpiginous borders that may be interrupted by fairly normal skin at one point, so that they form incomplete circles. They tend to fuse in time. In these geo-

graphic lesions tumorous nodules develop and break down, producing horrible fungating ulcers that give the disease the second part of its name. The first part is a misnomer, as it is not caused by mycotic organisms. Its nature is not understood; it resembles Hodgkin's disease, reticulo-endotheliosis, and lymphosarcoma, but is not proved to be any of the three.

In the first stage the microscope shows the banal perivascular sleeves of lymphocytes and an added feature in the form of eosinophils. This infiltration then becomes diffuse and spreads from the cutis into the epidermis. Swollen and often multinuclear fibroblasts appear and are a constant finding; mitotic figures are numerous. Many large cells resembling lymphoblasts and known as "mycosis cells" begin to appear, giving the lesion a neoplastic appearance like that of a malignant granuloma that is invading the epidermis and luxuriating beneath it. These giant lymphoblasts resemble the giant cells of Reed and Sternberg and may exhibit multinucleated forms. Lymphocytes are no longer prominent, but eosinophils are very much in evidence. The lesion may undergo involution and become cicatricized, or it may continue until the patient dies of the overwhelming toxemia produced by the ubiquitous sloughing sores.

DERMAL TUMORS

Epithelial. The epithelial tumors of the skin may be divided into noncancerous and cancerous groups, but such a division is clinical rather than histologic. It would be better to consider them as making up two general groups: one of these, which imitates the epidermis, is properly termed epidermoid; the other, which is highly characteristic but very puzzling, is usually called "basal-celled," but there are many reasons (to be discussed later) for rejecting this nomenclature.

EPIDERMOID TUMORS. PAPILLOMA OR VERUCA. There is some question as to whether this homely little tumor, the common wart, should be considered as a tumor at all. It

has a habit of disappearing and reappearing which is quite unlike other tumors, and its close resemblance to the lesions of hares infected with the Shope-Rous papilloma virus makes it seem highly probable that the papilloma, too, may be a viral infection. It usually appears on irritated surfaces such as fingers, hands, or other exposed parts; it seems to be aggravated by uncleanness. The grimy paw of the small boy is one of its favorite locations. It is grayish brown to dirty white and presents various shapes and sizes; it is covered with filiform papillae, and it may be flatter and smoother on occasion.

Microscopically it is characterized by the formation of tenuous, pointed papillae on its surface, which comprise piled-up keratinized cells of the horny layer. The bulk of the growth lies in the horny layer. The stratum granulosum may be thickened and its keratohyaline droplets enlarged and more numerous. Occasionally there may be some acanthosis or thickening of the rete malpighi, but this is more an attribute of the condylomas than of the papillomas. In elderly people the epidermoid papilloma may exhibit considerable metaplasia of its basal and spinous layers. That it may undergo frank malignant degeneration in such elderly subjects is not to be denied, but this does not often happen.

CUTANEOUS HORN. In these elderly subjects the proliferation of keratinized cells, or the lack of their desquamation, causes them to become heaped up and compacted into something that is so like a real horn that it cannot be told from one with the unaided eye. It may attain a length of several centimeters and a diameter of two or three. It often grows from the scalp, and one can well imagine what would have happened to an old woman unfortunate enough to produce one of these in the days of the "Salem witches" in Massachusetts. The picture revealed by the microscope gives the impression of a papilloma in which the papillae have become amalgamated into a single laminated mass of horny cells. At the

base of this there is marked increase in the thickness of the granular layer and more or less acanthosis accompanied with metaplasia of the rete and the basal layer. This gives the growth a bad reputation which does not seem to be completely justified in view of the good results obtained by simple

the yellow spots of the gross examination. There is no tendency for the growth to invade the corium, mitotic figures are present in the basal layer, where they are normally found, but not in abundance and not ectopically in the rete. Some of these seborrheic warts show a good deal of hyper-



Structure of surface of typical common wart, *verruca vulgaris*. Note filiform papillae and dense keratinized layer with very marked and untidy desquamation of scales.

wide removal of the horn bearing area about the base of the deformity.

SEBORRHEIC PAPILLOMA This is another relative of the epidermoid papilloma. It is more bulky than that tumor, apt to be sessile and gently rounded, and may often be deeply pigmented and mistaken for a melanotic mole. On the pigmented surface there are unappetizing yellowish spots about a millimeter in diameter, giving the growth a likeness to a poisonous mushroom. The sectioned surface of the growth shows the dots to be scattered all through it in the form of tiny sebaceous cysts. Under the microscope one finds a variable amount of hyperkeratosis, general thickening of the epidermis which is thrown into papillary folds in which are embedded epithelial "pearls" of desquamated keratinized cells, these are

keratosis, which may go over to the formation of papillae similar to those of the *verruca vulgaris* that we have just considered.

PLANTAR WART The flat or slightly papillary wart that develops on the sole of the foot is a combination of callosity and *verruca*, there is rather more papillary keratosis than in the corn, which tends to have a smooth surface. The granular layer is much thickened, and there are often inclusions in its cells. These bodies stain deeply with fuchsin or orange G and resemble the inclusions of molluscum contagiosum to a certain extent, they are also similar to the "corps ronds" of Darier's disease (which will not be discussed here). There is a known association between plantar wart and trichophytosis, and those warts showing marked production of such

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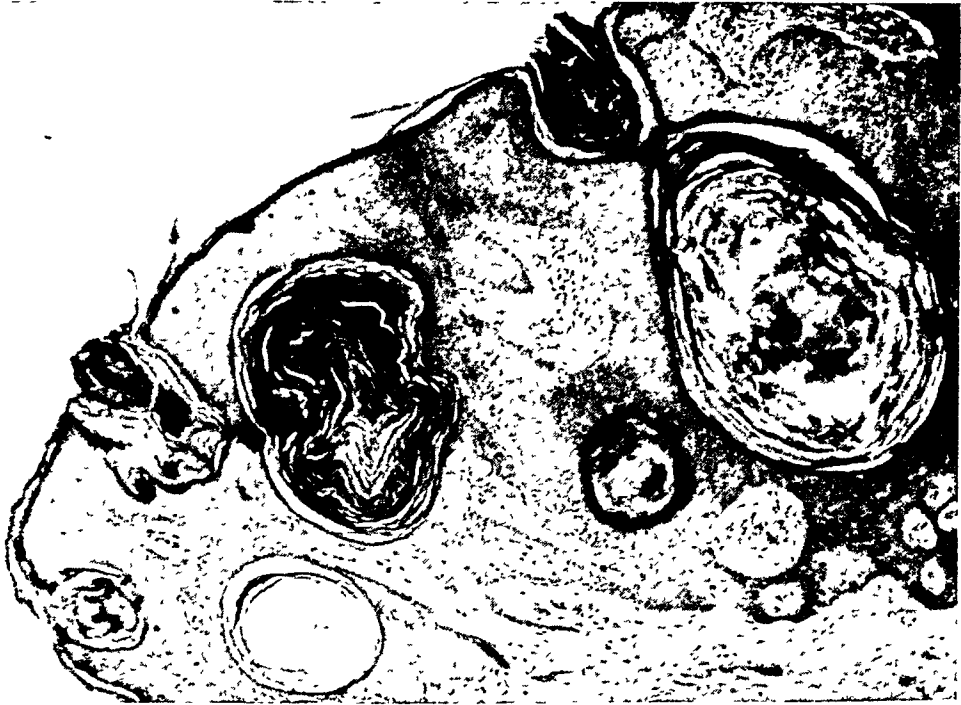
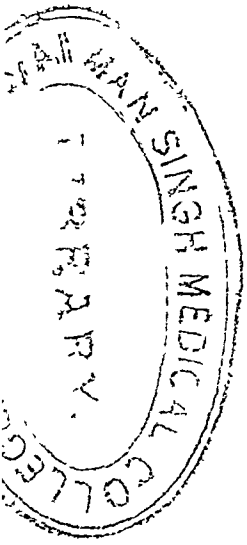
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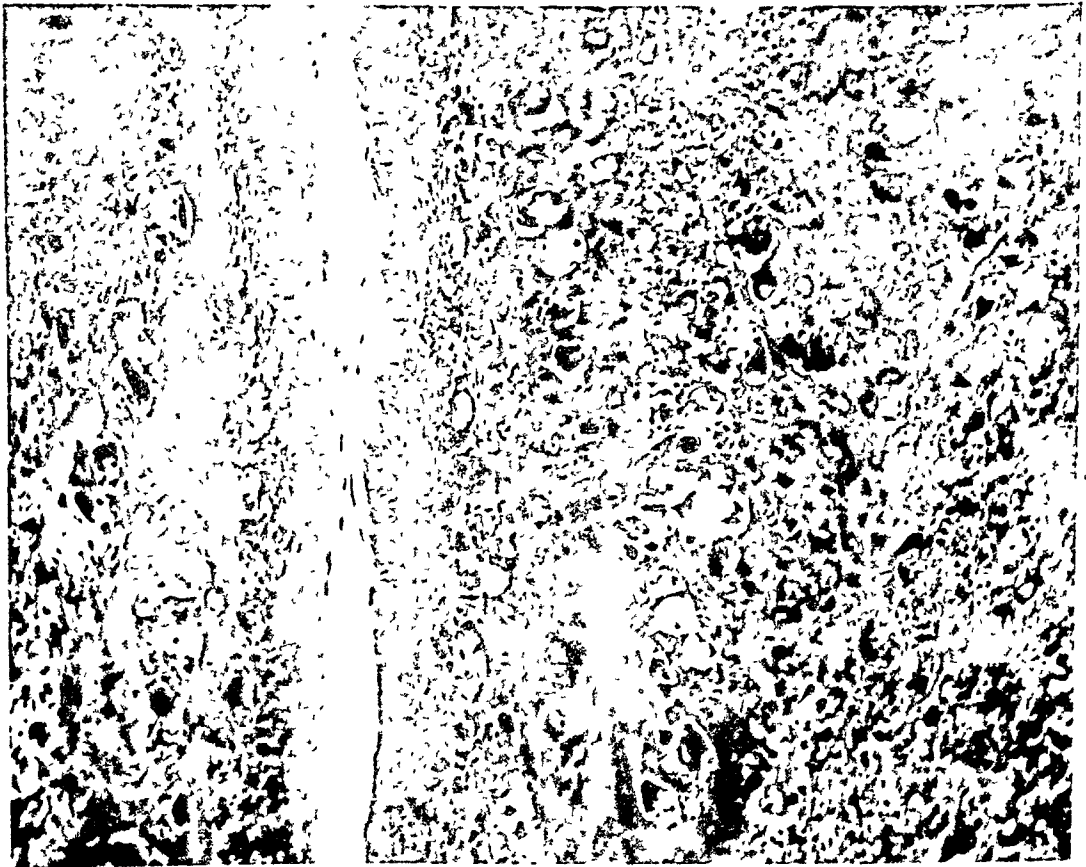
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Section from surface of typical seborrheic wart or papilloma. Note collections of laminated, keratinized cells within pseudocysts. On gross examination these appear as small, yellowish spheroids of pul-taceous material.



Dense keratinized surface of plantar wart of the true variety. Many plantar warts are clavi or "corns." This one is papillary and exhibits many "corps ronds"—deeply eosinophil inclusion bodies that resemble those in molluscum contagiosum but are more like those of Darier's disease, as well as those of some common "warts" of the "infectious" variety.

sinophil bodies may represent viral infections on the basis of their appearance. This is frankly a surmise on the part of the writer, it has yet to be demonstrated as true.

CALCIFYING EPITHELIOMA. A rather rare and confusing tumor that is more or less neglected in the textbooks is the calcifying epithelioma. It grows very slowly, is usu-



Low powered view of calcifying epithelioma in which black masses are calcium salts, dense gray ones are bony spicules developing from calcified epithelium (much as do the teeth), and lighter masses with black dots at their periphery are epidermal islands. This is a non malignant growth.

ally mistaken for some sort of cyst, and may develop anywhere in the skin. It has been observed in children as well as in adults. It is adherent to the surrounding tissue, and after removal it is found to be stony hard, as it is heavily impregnated with salts of lime; this is no wonder. Its microscopic appearance is strikingly similar to that of an epidermoid carcinoma, but it exhibits few mitotic figures and there is extensive calcification of its pearls. This may even go over into ossification. There are cysts in the epidermal plugs that result from degeneration of the cellular tissue. Keratin is very heavily deposited in the upper layers and in the prickles cells of the rete as well. This tumor has recently been

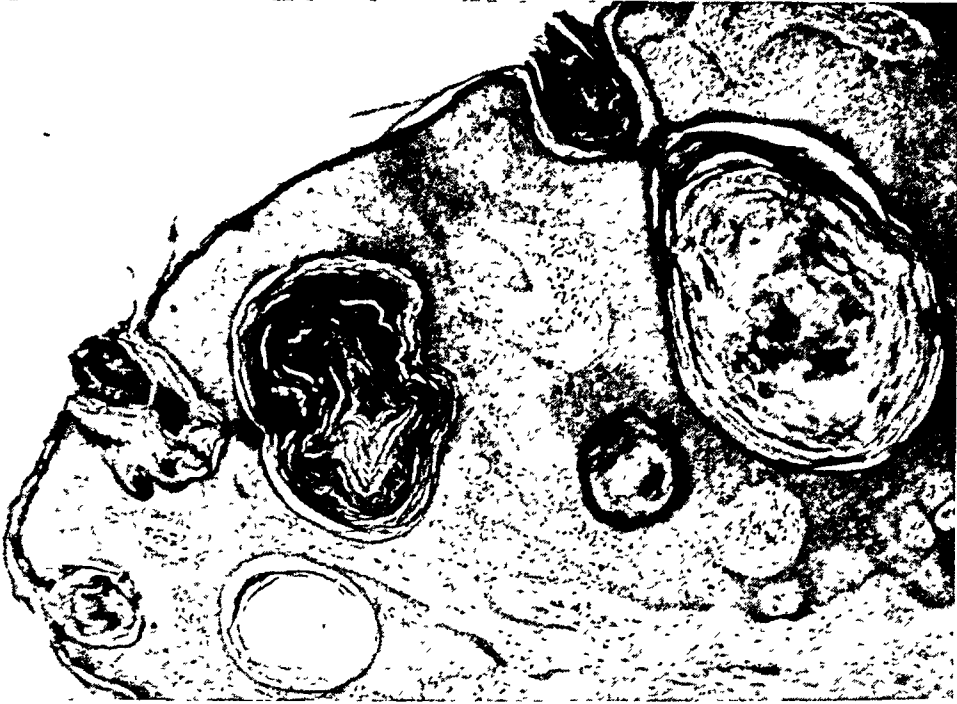
well discussed by Highman and Ogden. It is chiefly of importance as representing an innocent growth that has sometimes been mistaken for a spontaneous regression in an epidermoid carcinoma. This it does not appear to be.

"PRECANCEROUS DERMATOSES." Bridging the gap between normal skin and dermal cancer are three diseases that approach this very closely without actually representing it in its epidermoid or "squamous celled" form. These are keratosis senilis and Paget's and Bowen's diseases.

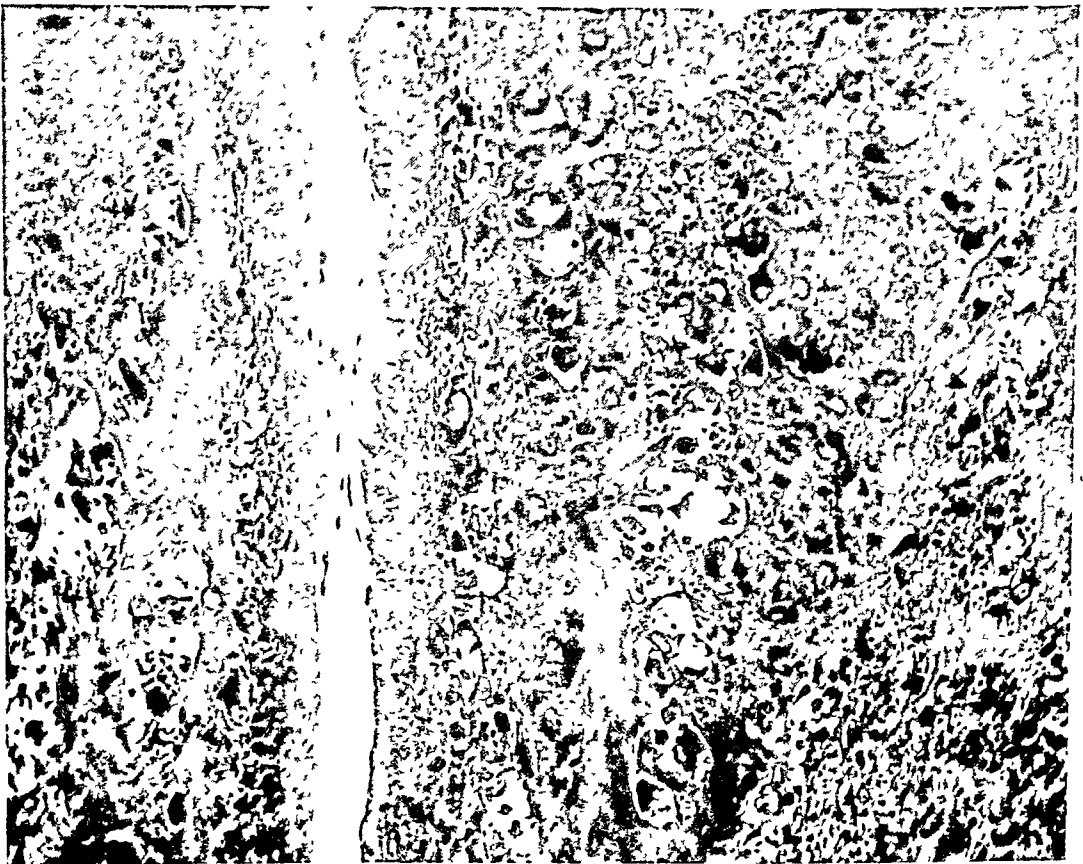
Keratosis Senilis. In the very old there develop patches of pigmented, freckle like skin a few millimeters in diameter and covered by horny scales. Microscopically there is hyperkeratosis and an atrophy of the skin underlying these areas, with foci of inflammation and atypia of some of the epithelial elements, which become large and have correspondingly large and hyperchromatic nuclei. This is often associated with the development of the metaplastic verrucae that were spoken of under the papillomas and are known as "verrucae senilis."

Paget's Disease. Best known and most frequently observed in the nipple (see Chapter 19) this disease may develop elsewhere on the scrotum, penis, anal region, back, neck or buttocks. Following an eczematoid eruption large areas of wet, encrusted lesions that may be single or multiple develop in the skin. These are microscopically characterized by the presence of large pale cells in the rete malpighi and basal layer that possess very large nuclei. They tend to loosen the texture of the epidermis, as does the edema with which they are associated, so that a characteristic disintegration of the rete cones sets in which makes them appear like glandular cysts containing desquamated lining cells. There is considerable hyperkeratosis, but the crusts are granular rather than scaly.

Bowen's Disease. Somewhat similar to Paget's disease, this condition belongs with the hyperkeratoses, it develops slowly and forms single or multiple papulosquamous



Section from surface of typical seborrheic wart or papilloma. Note collections of laminated, keratinized cells within pseudocysts. On gross examination these appear as small, yellowish spheroids of pul-taceous material.



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An early stage of epidermoid carcinoma of the skin. Note keratinized "pearls," multiple and irregular rete cones with metaplastic basal cells, and the fact that these are not as yet straying into corium. There is a heavy superficial layer of desquamating keratinized cells.

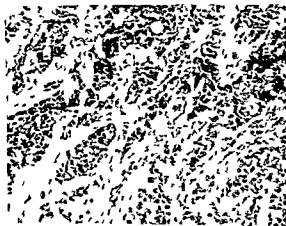
guard by indicating the possibility of the development of carcinoma without implying its inevitability. Thus it is well to excise these lesions widely or to destroy them thoroughly by fulguration or caustic applications of the x ray.

EPIDERMOID CARCINOMA. We come at last to the epidermoid carcinoma, which may develop anywhere on the skin or mucous membranes resembling skin and having an epidermoid architecture. It may appear spontaneously, as on the bridge of the nose, or be induced by chemical or mechanical irritation (chimney sweeps' carcinoma). There is a group of these tumors induced by such irritation—the carcinoma of Kashmiri who carry small charcoal heaters over the abdomen for warmth to warm them—the "Kairo cancers" of the Japanese who have a similar practice—pipe smoker's cancer, and many other examples.

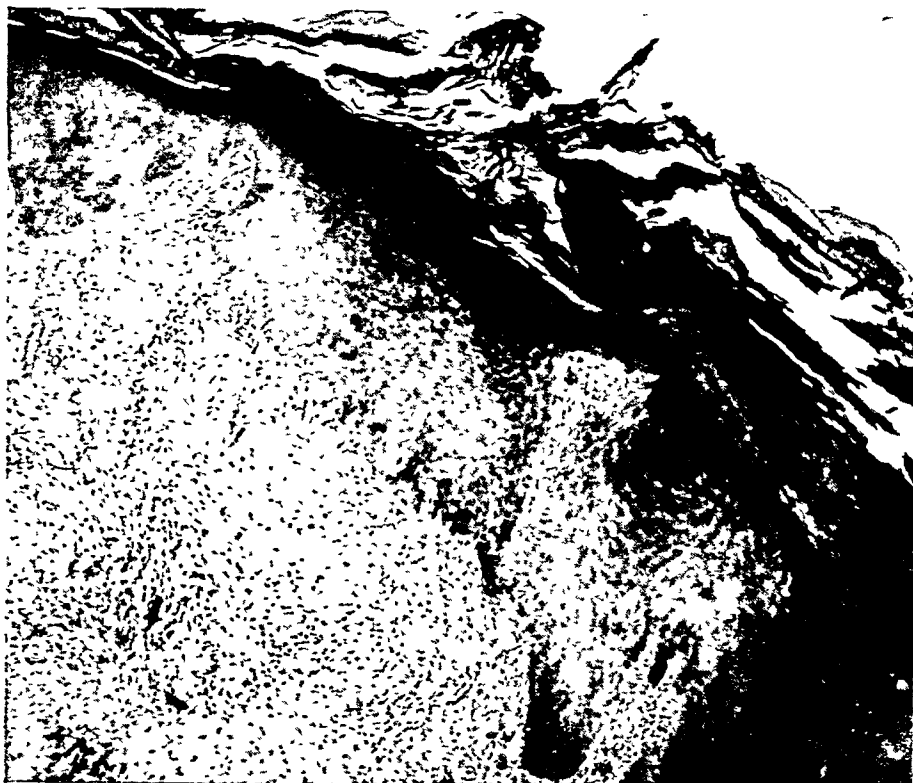
The tumor grows from a very unostentatious dry and sluggish ulcer that is shallow and spreads until it is converted into an unmistakable ulcer with very hard edges and

an irregular outline. It is usually not inflamed until it becomes secondarily infected.

Microscopically there is an enormous and irregular thickening of all the layers of the epidermis. The hyperkeratosis of the surface is usually complicated by a deep keratosis that produces pearls of keratinized



Plexiform epidermoid carcinoma of skin which grows in an anastomotic plexiform manner and fails to undergo much keratinization. Instead it spreads more rapidly than the keratinizing variety and is therefore a more malignant growth.

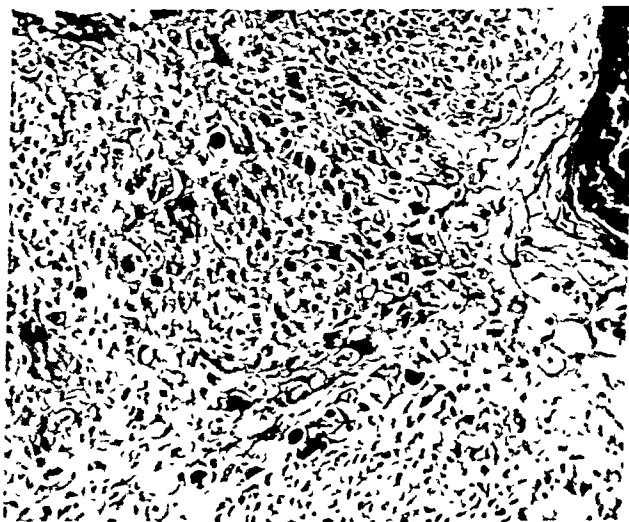


Lesion of senile keratosis. Note almost neoplastic thickening of epidermis, marked hyperkeratosis and desquamation. Stratum granulosum is as thick as it would be in a wart or corn—all part of the dyskeratosis. There is also diffuse chronic inflammation of corium.

tumor-like masses that become eroded and covered with crusts. These tend to be arranged into groups, and while they may cause metastasis to the regional lymph nodes, this is unusual. The microscopic picture consists in tumor-like areas of thickening in an otherwise atrophic epidermis. In these areas there is great irregularity of the rete cones, which may become ballooned out into large structures that may fuse with neighboring cones in a reticular fashion. Here the arrangement of the cells becomes very disorderly, and there appear many gigantic globoid cells that lie in the rete malpighi. These are typical neoplastic giant cells and may exhibit the abnormal mitoses common to this type of monstrosity. Unlike Paget's disease, this lesion exhibits very little edema, nor are the rete cones disintegrated and broken up, though they are much disarranged. In this disease, as in other dyskeratoses, there are numerous acidophile globular inclusions in the cells reminiscent of those of molluscum contagiosum.

Prognosis of Precancerous Dermatoses.

Any of these three lesions may become frank carcinoma, but not necessarily so. The term "precancerous" is undesirable in many ways, but it serves to put the physician on his



Typical area from skin in Bowen's precancerous dermatitis. Note large number of neoplastic giant cells, vacuolization scattered throughout epidermis, and general lack of orderly arrangement of the rete malpighii.

is often known as a "cylindroma" (This is because of the fancied similarity of the cross sections of the trabeculae to hyaline urinary casts, the German for which is "Cylindrom") If the masses of cells tend to break down centrally and to form pseudocysts the tumor is known as "epithelioma adenoides cysticum" to which the names of Brooke and Fordyce are often attached. Mitotic figures are not numerous, and there is no tendency either to ulcerate the overlying epidermis or to invade the underlying tissue. The cystic variety is more common on the eyelids or nose, and it may be familial, the cylindroma is usually located upon the scalp.

The interpretation of the tumor is confused. Because of the surrounding layer of basal cells from which the central cells apparently develop, it is usually known as a "basal celled tumor." That it may represent an abortive attempt to form hair follicles or other dermal adnexa such as sweat glands is a matter that will be discussed presently.

Hair matrix (Basal celled) Carcinoma (Rodent Ulcer) Krompecher gave this tumor the name "basal celled carcinoma," and it has stuck. The growth is apt to arise on the face (the nose and adjoining cheeks being a favorite starting point), but it may develop anywhere on the skin. In its early stages it is difficult to distinguish from an early epidermoid cancer, but it is less scaly and even more indefinite in its ulcerative tendency. Once started, however, and after ulceration has begun in earnest, the tumor erodes everything in its path, including bony tissue, for that reason it used to be called "rodent ulcer." It is a malignant growth, but in its initial stages so mildly so that its early removal is seldom followed by recurrence, and metastasis is very unusual and seen only in neglected and far advanced instances.

Krompecher described no less than six types of this tumor, but they are all mere variations upon the same theme. They may be composed of solid nests of cells connected with the overlying epidermis at one

or more points, or they may develop multicentrically. The nests of cells are not as regular as they are in the nonmalignant cylindroma, but are more serpiginously outlined and geographic. They present the same radially directed limiting basal layer of cylindrical cells, but these may sometimes stray into the corium in which they are situated. Mitotic figures are variable in a



Metastasis in lymph node of a hair matrix carcinoma, this is a very rare occurrence. A lymphoid follicle is above at left, while below are interlacing cords of neoplastic invading cells.

series of tumors and may be seen in the central cells as well as in the basal layer. Some of the tumors tend to break down and form pseudocysts like those of the epithelioma adenoides cysticum, these are often noted in such tumors when they occur on the extremities, and Ewing considered that they boded ill for the prognosis. One variety tends to form small globular growths in the cutis and epidermis that are raised into mole like structures. Other variations have been noted, among them the presence of hyaline trabeculae like those of the cylindroma ("malignant cylindroma").

Long ago Frank Mallory recognized these tumors as less malignant than the epidermoid variety, although they were called "basal celled." Now the basal cell is the least differentiated of all the dermal ele-

cells. The growth may take an acanthomatous form, with marked thickening of the rete malpighi and metaplasia of its cells, which contain many mitotic figures. In other examples there is overgrowth of the basal layer in a downward and infiltrating fashion, with the formation of a reticular pattern of thinned-out cords of basal cells (plexiform epidermoid carcinoma). In diag-

accompanied by a dissection of the regional chains of nodes in order to remove any possible metastatic focus.

"BASAL-CELLED TUMORS." Of these there are a number of types which could be simplified if we knew more concerning their true nature. The nonmalignant varieties are apt to form small mushroom-like tumors on the skin (often on the scalp) that are sup-



Section from benign cystic epithelioma of adenoid appearance (epithelioma adenoides cysticum benignum). This tumor might be a more solid form of cystic papilliferous hidradenoma.

nosing the tumor the integrity of the basal layer is an important factor; if its cells are infiltrating the corium in groups of two or three or feathering out into that layer one must consider even an otherwise nonmalignant-looking tumor to be malignant.

Epidermoid carcinoma, then, may be chiefly keratinized and mildly malignant, chiefly acanthomatous and decidedly so, or chiefly plexiform and composed of cells of the basal layer. To call this a "basal-celled carcinoma" would be confusing, as we shall see presently, but that is what it actually is, and it constitutes the most malignant of the three subvarieties. This tumor tends to metastasize to the regional lymph nodes, so that removal of the carcinoma should be

ported on broad pedicles. They are smooth, rubbery in consistence, and, on section, may show whitish dots not unlike those of the seborrheic warts. These lie in a light-brown, homogeneous background.

Microscopically they are composed of spherical or cord-like masses of indifferent cells that are polygonal, rather pale, loosely set, and surrounded by a sheet of radially directed columnar basal cells that encloses them in a capsule of epithelium that is, in turn, surrounded and enclosed in a sheet of hyaline connective tissue which sends trabeculae into the center of the mass. When the hyaline sheath and trabeculae are prominent and the cells do not tend to break down in the center of the masses, the tumor

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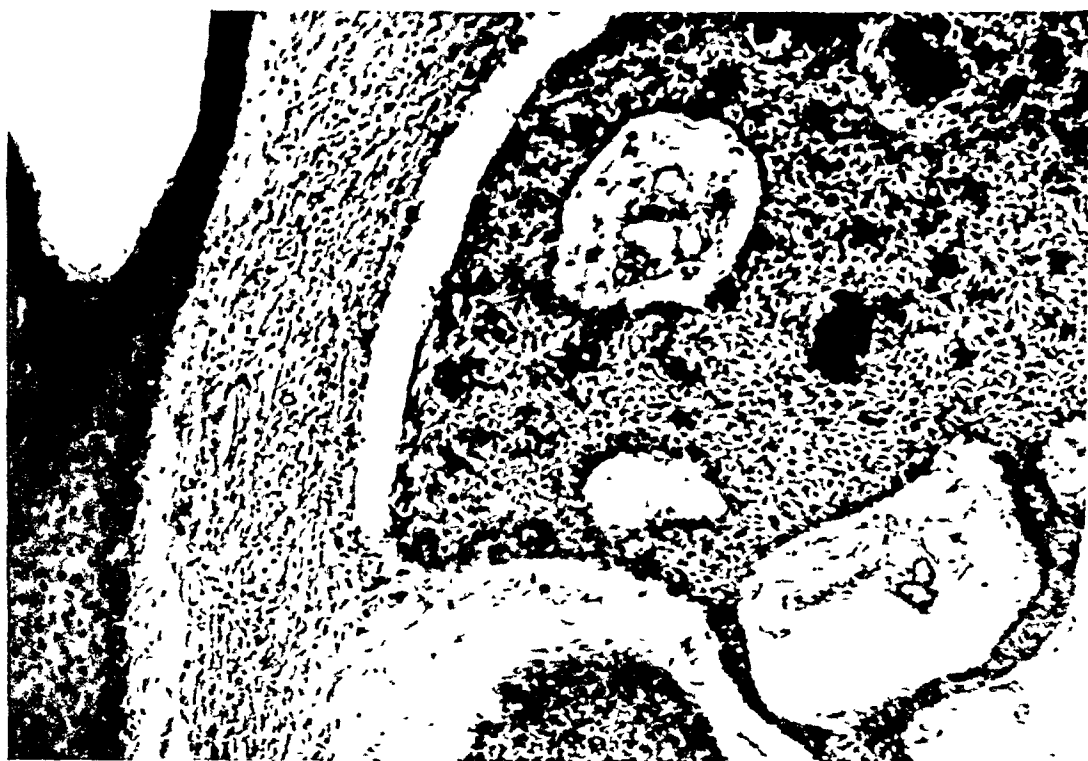
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Microscopically they are composed of spherical or cord-like masses of indifferent cells that are polygonal, rather pale, loosely set, and surrounded by a sheet of radially directed columnar basal cells that encloses them in a capsule of epithelium that is, in turn, surrounded and enclosed in a sheet of hyaline connective tissue which sends trabeculae into the center of the mass. When the hyaline sheath and trabeculae are prominent and the cells do not tend to break down in the center of the masses, the tumor

is often known as a "cylindroma" (This is because of the fancied similarity of the cross sections of the trabeculae to hyaline urinary casts, the German for which is "Cylindrom") If the masses of cells tend to break down centrally and to form pseudocysts the tumor is known as "epithelioma adenoides cysticum" to which the names of Brooke and Fordyce are often attached Mitotic figures are not numerous, and there is no tendency either to ulcerate the overlying epidermis or to invade the underlying tissue The cystic variety is more common on the eyelids or nose, and it may be familial, the cylindroma is usually located upon the scalp

The interpretation of the tumor is confused Because of the surrounding layer of basal cells from which the central cells apparently develop, it is usually known as a "basal celled tumor" That it may represent an abortive attempt to form hair follicles or other dermal adnexa such as sweat glands is a matter that will be discussed presently

Hair matrix (Basal celled) Carcinoma (Rodent Ulcer) Krompecher gave this tumor the name "basal celled carcinoma," and it has stuck The growth is apt to arise on the face (the nose and adjoining cheeks being a favorite starting point), but it may develop anywhere on the skin In its early stages it is difficult to distinguish from an early epidermoid cancer, but it is less scaly and even more indefinite in its ulcerative tendency Once started, however, and after ulceration has begun in earnest, the tumor erodes everything in its path, including bone tissue, for that reason it used to be called "rodent ulcer" It is a malignant growth, but in its initial stages so mildly so that its early removal is seldom followed by recurrence, and metastasis is very unusual and seen only in neglected and far advanced instances

Krompecher described no less than six types of this tumor, but they are all mere variations upon the same theme They may be composed of solid nests of cells connected with the overlying epidermis at one

or more points, or they may develop multicentrically The nests of cells are not as regular as they are in the nonmalignant cylindroma, but are more serpiginously outlined and geographic They present the same radially directed limiting basal layer of cylindrical cells, but these may sometimes stray into the corium in which they are situated Mitotic figures are variable in a



Metastasis in lymph node of a hair matrix carcinoma, this is a very rare occurrence A lymphoid follicle is above at left, while below are interlacing cords of neoplastic invading cells

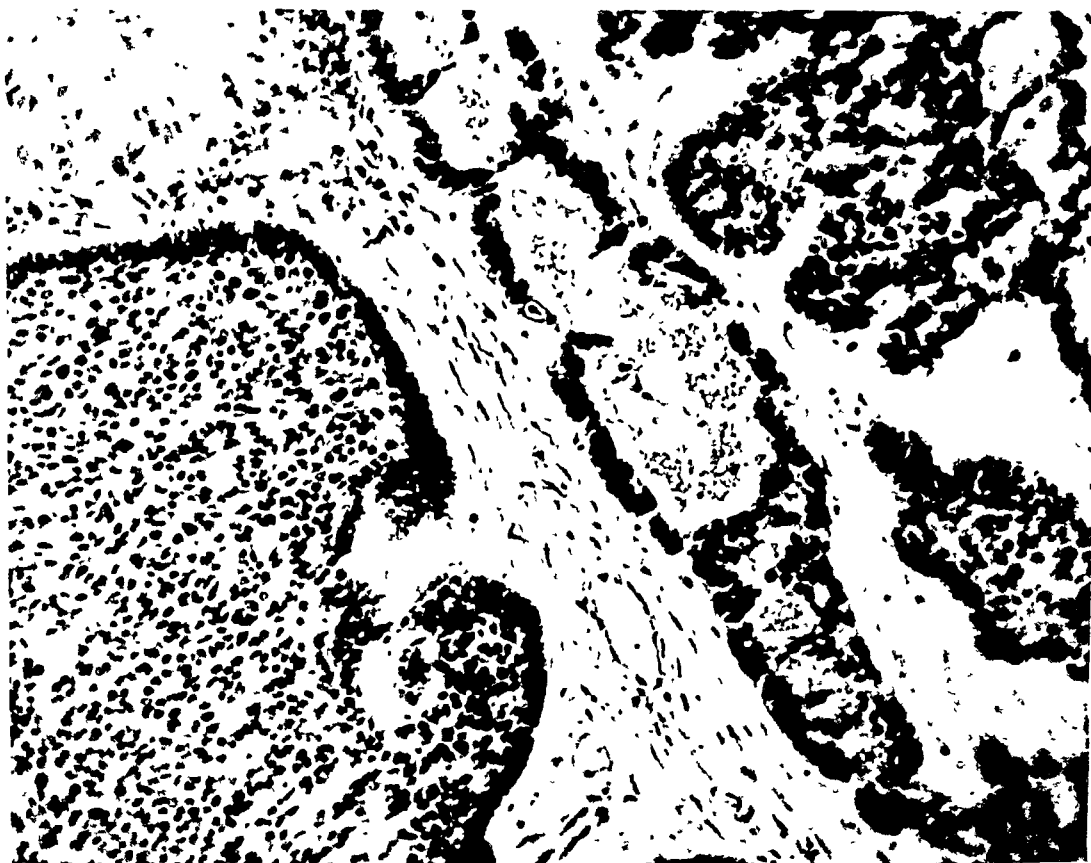
series of tumors and may be seen in the central cells as well as in the basal layer Some of the tumors tend to break down and form pseudocysts like those of the epithelioma adenoides cysticum, these are often noted in such tumors when they occur on the extremities, and Ewing considered that they boded ill for the prognosis One variety tends to form small globular growths in the cutis and epidermis that are raised into mole like structures Other variations have been noted, among them the presence of hyaline trabeculae like those of the cylindroma ("malignant cylindroma")

Long ago Frank Mallory recognized these tumors as less malignant than the epidermoid variety, although they were called "basal celled" Now the basal cell is the least differentiated of all the dermal ele

ments and is therefore the most likely to produce tumors that are more malignant than those resulting from the multiplication of less dedifferentiated elements. This is true of the "plexiform epidermoid carcinoma," which is made up of rapidly growing basal elements. Why, then, should the

ments of the matrix of the hairs, particularly the "roots," and this is the case. The tumors are also very similar to the hydradenomas (see later) from which they might well be derived.

When one of these has developed into a rodent ulcer of long standing, one may find



Very glandular portion of hair-matrix or basal-celled carcinoma of skin. Such areas strongly suggest connection with sudoriferous rather than with pilar or basal apparatus of epidermis. Note conventional solid arrangement at left and glandular structures at right. These contain some sort of coagulated secretion.

so-called "basal-celled carcinoma" be less malignant than these? In the cellular masses of some of these tumors Mallory noted the presence of abortive hair shafts: bits of amorphous keratinized material like fragments of hair. He therefore deduced that these tumors originate in hair matrices and called them "hair-matrix carcinomas"—an assumption which is strengthened by the fact that they are sometimes seen to be associated with sebaceous glandular elements. This hypothesis demands that the type-cell of the tumor should appear to be entirely similar to the more primitive ele-

epidermoid carcinoma growing in the margin of the ulcer.

Tumors of Dermal Adnexa. Having discussed growths of the skin proper, we now come to those of its adnexa. Of these there are several, besides the cysts, which are not true tumors and will be taken up first.

CYSTS OF THE SKIN. Epidermal Cysts. These lie in the corium, seldom deeper, usually arising at the openings of the ducts of sebaceous glands and hair follicles. They rather closely resemble the sebaceous variety (discussed below), though they have thinner walls. They may contain fragments

of hair, probably they are attributable to developmental displacement of epidermis. (Similar cysts may result from the forcible introduction of bits of epidermis into the corium or subcutaneous tissue as a result of trauma with rather blunt instruments, forcing the hand down upon a sharp stone, or similar injury. They have been discussed under Epithelization in the chapter on Healing of Surgical Wounds.)

Sometimes epidermal cysts are very difficult to identify. They seldom undergo malignant transformation.

Dermoid Cysts These are usually found near natural embryonal clefts, where there is opportunity for their lining to become buried in the deeper tissue as it grows around them. They exhibit some or all of the dermal adnexa and contain oily, pulsataceous material such as one finds in the ovarian dermoid teratomas, like which (being in the nature of teratomatous embryonal rests) they may occasionally show such extraneous elements as teeth, bone, or cartilage.

Pilonidal Sinuses and Cysts A very common form of dermal cyst attributable to congenital developmental defects is the pilonidal sinus, along the course of which a cyst or cysts may develop. This defect gives very little external evidence of its presence, there is usually a small dimple over the coccyx in the internatal sulcus, and at the bottom of this depression one may observe the opening of a sinus 1 or 2 mm in diameter. The patient seldom discovers that there is such a tract until it becomes infected and causes acute symptoms.

The cause of pilonidal sinuses and cysts is probably the traction exerted upon the skin at the site of the involuting neural canal when this, together with the tail bud, retracts. This produces a form of traction diverticulum in the overlying integument. The sinus proper is usually about 2 to 4 cm in length and may widen out to produce a cyst 1.5 to 2.0 cm in diameter. This is filled with soft, grumous, brown gran-

ulation tissue containing a variable amount of matted hairs. When such hairs are found in the sinus, however, they are not matted, instead they are grouped into a fascicle or penicilliary bundle like a small paintbrush. On account of these hairs the defect is known as a "pilonidal" (nest of hairs) sinus.

The microscopic appearance of such a sinus is not particularly interesting, the epithelial lining which bears the hairs is



Granulation tissue from pilonidal cyst. A fragment of hair shaft is seen in transverse section at upper right. The black disc is a mass of calcium.

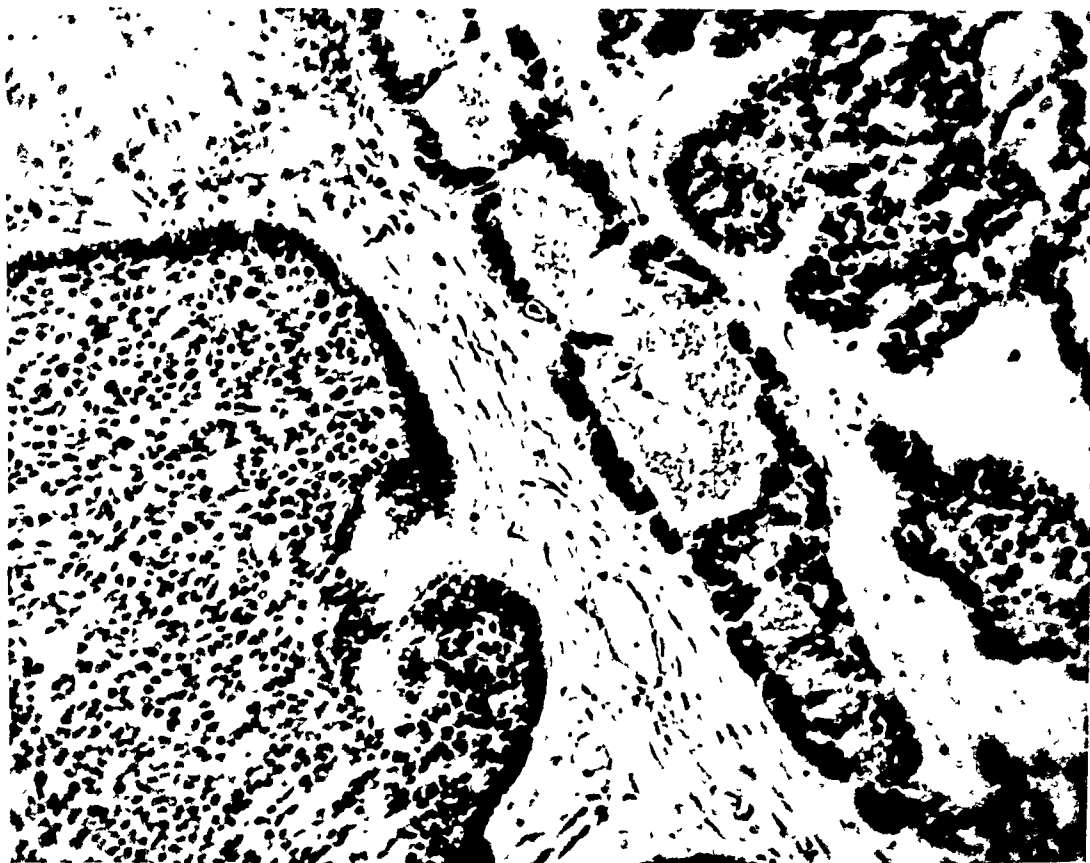
usually found to have disappeared and to have been replaced by granulation tissue of a banal type in which fragments of hair are entangled. The follicles from which these have developed are seldom demonstrable. As the malformation never exhibits neural elements, this bears out the assumption that it is dermal in origin and not a form of myelocoele, as one is often led to infer from the literature. The importance of pilonidal sinuses and cysts lies in their propensity to become infected during early adult life.

If the infection should penetrate the wall of the structure it will produce an abscess or a local cellulitis that may be quite extensive and painful. As the tissue surrounding the sinus and cyst is largely adipose, such infection readily spreads through it. Owing

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granulo-sum, with coarsening of its granules of keratohyalin. The rete malpighi is usually negligible, being much thinned out. The basal layer is unremarkable and forms the outer layer of the cyst's wall. The sebaceous cells that should be clustered in lobules about the duct are usually absent, having atrophied and disappeared. As we have



Epidermoid carcinoma developing in wall of sebaceous cyst of many years' standing. Upper strip of epidermis represents overlying skin, while lower one shows carcinomatous proliferation of epidermis lining the cyst. At bottom are masses of keratinized cells that constitute the curdy contents of all sebaceous cysts.

seen, sebaceous glands are very vulnerable and readily degenerate and disappear under slightly adverse conditions.

On rare occasions there may be malignant degeneration in the wall of the cyst which transforms it into an epidermoid carcinoma, but this feature has been overstressed in some books. In the course of inspecting hundreds of these cysts this phenomenon (fortunately for the patients) is very uncommonly encountered. When a sebaceous cyst exhibits a thick, horny wall that is poorly demarcated from the surrounding connective tissue, with contents that are also horny and dry, it is always well to cut sections and examine them for microscopic evidence of malignant degeneration.

Hyperplastic Conditions of Sebaceous Glands. A simple hyperplasia and hypertrophy of sebaceous glands, usually on the skin near the inner canthus of the nose, or over its bridge, has long gone under the name of "adenoma sebaceum." Its structure is not that of an adenoma, and it differs sharply from that of the true sebaceous adenoma, which is very rare. These so-called "sebaceous adenomas" are small, yellowish, raised areas a few millimeters in diameter that resemble moles in their appearance. Under the microscope they reveal simply a concentration of sebaceous glands and hairs in a small, circumscribed area of the skin. These focal hyperplasias may occur anywhere on the body and are particularly numerous in Pringle's disease, which commonly accompanies von Recklinghausen's neurofibromatosis.

SEBACEOUS ADENOMA. The true sebaceous adenoma is a rare growth characterized by its microscopic picture, which reveals numerous complexes of overgrowing, redundant sebaceous glandular tissue that shows few or possibly no ducts and has a distinctly neoplastic appearance. The growth is rounded, circumscribed, soft, and nonulcerating. Warren and Warvi, in an excellent paper on this subject, report five cases, of which three were taken from parts of the head and two were of unknown origin, being unaccompanied by histories. The microscopic picture has already been suggested in the defining of the tumor's nature. It is composed of large, clear, sebaceous cells that are arranged in lobular masses and tend to stain more deeply near the periphery of these than in their more central portions. They should not exhibit mitotic figures. They are in no way metaplastic, and the tumor should be readily recognized by its typically sebaceous architecture and lack of ducts.

SEBACEOUS CARCINOMA. Carcinoma may develop in sebaceous glands and if it is very metaplastic it may be difficult to recognize unless a portion of it retains some of the

to the fact that the sinus often branches and forms short diverticular cul-de-sacs in the adipose tissue it is imperative that it be thoroughly excised if a permanent cure is to be effected. The excision is usually in the form of an ellipse that is bisected by the median raphe of the internatal sulcus. The sinus generally opens to one side or

consequence of such stoppage there is an accumulation of desquamated keratinized epithelium in the lumen, with an accompanying dilatation of the duct which may thin out its wall but more often results in thickening, with the acquisition of a horny consistence. The cysts are usually only a few millimeters in diameter, but in the case



Sagittal section of an entire microscopic sebaceous cyst to demonstrate the genesis of such cysts. It is entirely a matter of retention in an obstructed duct of a sebaceous gland.

the other of this raphe, extends parallel with the integument, and ends near the fascia over the sacrum. Therefore the ellipse should be sufficiently large and deep to include the entire sinus with its ramifications and to penetrate to the sacral fascia. The rather large defect is not difficult to close, as the healthy tissue soon forms granulation tissue that is epithelized.

Sebaceous Cysts. The sebaceous cyst (known in common parlance as a "wen") is one of the commonest lesions to be excised in the dispensary and sent to the laboratory. It is the soft, sometimes large cyst that so often appears on the scalp, face, or neck. It represents the result of stoppage in the secretory duct of a sebaceous gland. In

of timid, stubborn, or indifferent subjects they may attain several centimeters. They are covered with smooth skin, and on section they are found to contain curdy material that varies in appearance from that of cottage cheese to a rather dry, light-brownish, and scaly consistence. This accumulation often gives off an unpleasantly rancid odor.

Under the microscope the structure is seen to be composed of a wall of very thick epidermoid epithelium surrounding many layers of keratinized cells that are sometimes very compact, at other times loose and scaly. Occasionally they may become calcified. There may or may not be considerable thickening and prominence of the stratum

vascular, and it tends to bleed inordinately at operation. Microscopically the epithelium is characteristically arranged into cavernous spaces that have very much the appearance of those of a lymphangioma. It is arranged in an inner secretory and an outer myo-epithelial layer, but it may become quite redundant and heaped up in places. The cavernae contain a scanty granular coagulum that is precipitated from the fluid in

'cylindroma.' It is so frequently misdiagnosed, although it is the commonest form of sudoriferous tumor, that it deserves some what detailed consideration. It may be solitary or in discrete multiple groups, when it occurs on the scalp it may be pedunculated and mushroom like. It rarely exceeds 4 cm in diameter. When it is cut through it is found to be light brownish and very succulent, dripping clear fluid.



Duct celled type of hydradenoma cysticum papilliferum. This one represents overgrowth and dilatation of sudoriferous ducts.

them during fixation. There are two types of growth, one proliferative and the other degenerative, which give rise to two general forms of tumor. In the former there is an increase in epithelium, in the latter an increase in stromal tissue which grows into the spaces as plugs of connective tissue in such a way as to produce a picture strikingly resembling that of intracanalicular fibroadenoma of the breast. There may be two subvarieties of this tumor: a superficial type affecting the ducts primarily, and an intermediate one forming branching tubular structures that usually occupy the upper or middle layers of the corium.

Hydradenoma. A solid, rather than a definitely glandular tumor, this closely resembles the epithelioma cysticum and is usually grouped with it under the name

Microscopically it is composed of alveolar masses of compactly arranged cells that occasionally form central lumina lined by cylindrical or cuboidal epithelium. The cytoplasm of the component cells may be eosinophil or pale, with orange G there is a rather spotty staining of the central portions of the alveolar masses that hints at partial keratinization of the cells. The cells often form closely applied coiled cords or chains that lie roughly parallel within the alveolar masses. The tumor lies in the corium, not apparently intimately connected with the epidermis, although some of its peripheral cellular groups may be observed abutting directly upon sudoriferous ducts, as though connected with them. Around the periphery of each cell mass there may be no palisading of the basal layer, or it may be

architectural characteristics of the parent gland. Grossly it appears to develop in an adenoma which has persisted for a long time, and when one of these begins to ulcerate, expand, and invade the surrounding tissue one is amply justified in considering the probability of carcinomatous change. Sebaceous carcinoma is occasionally observed in connection with hair-matrix car-



Typical field from syringocystadenoma. This is questionably a tumor and more probably represents a developmental defect or an obstruction of sudoriferous ducts.

cinoma, which is added proof of Mallory's assumption that this is a tumor of dermal adnexa, rather than of simple basal cells. Sebaceous carcinoma not infrequently metastasizes. Warren and Warvi present a copious list of references on this subject.

Tumors of Sudoriferous Glands. **TUMORS OF ECCRINE GLANDS.** These tumors have been well described and catalogued by Gates, Warren, and Warvi, and their systematic presentation will be drawn upon here. There are three categories of gland to be considered: the ordinary eccrine sweat gland; the apocrine variety which secretes the pungent sweat that has occasioned the coining of the too-familiar term "body odor" or "B.O."; and the specialized glands that resemble sudoriferous structures histologically, but produce an entirely different se-

cretion. All of these are dermal adnexa. The tumors that they produce were for long confused with other varieties and miscalled "angiomas," "lymphangiomas," or "endotheliomas" of various types. They are divisible into four types: syringoma, hydradenoma papilliferum, hydradenoma, and hydradenoid carcinoma.

Syringoma. When single, these tumors may attain a few centimeters in diameter, but they are usually multiple and measured in millimeters. They are slightly elevated, slightly yellowish or brownish, translucent on section, and covered by smooth skin. They are most frequently found over the chest or in the axillae. Their microscopic appearance is characteristic, presenting small groups of epithelial cells that constitute compressed and collapsed ducts with a terminal, cystic expansion lined by flattened epithelium. They are quite innocuous and supposedly represent fetal malformations.



Cystic and papillary form of hydradenoma (h. cysticum papilliferum). This is often mistaken for lymphangioma.

Hydradenoma Papilliferum. This is larger than the preceding tumor, is found on the labia and perineum and over the groins and thighs. It is gently domed, rather boggy on palpation (tending to pit on pressure) and may measure several centimeters in diameter. On section it is spongy and brownish, exuding a clear yellowish-brown fluid. The tumor is, at the same time, very

regular and marked. Each mass lies within a hyaline collagenous sheath, and there are trabeculae of the same hyaline material within the cellular aggregations. Cross sections of these look like casts, hence the German name "Cylindrom," from which we get "cylindroma."

Hydradenoid Carcinoma The commonest form is solid and probably represents malignant transformation of a hydroadenoma, this explains the apparent variation in some of the "basal cell" carcinomatous types. Other forms may apparently develop from the other types of sweat gland adenoma, particularly the papilliferous type. Naturally, it will be found that there are resemblances to certain carcinomas of the breast, as the glands from which both originate are very similar. That the so-called "sweat gland carcinoma" of the breast originates from sudoriferous glands in the depths of that organ is denied by Warvi and Gates, an opinion concurred in by the writer (See under "Tumors of the Nipple" in chapter on the breast.) Carcinoma of the hydradenoid type is not very malignant and usually causes late metastases.

TUMORS ATTRIBUTED TO SUDORIFEROUS ORIGIN Concerning the so-called "turban tumors" of the scalp there is so much diversity of opinion that it would be better to await further study of the matter before committing oneself. They are familial, arise along the hairline on the forehead as soft, nodular, nontender tumors that gradually encroach upon the scalp above that line. They have been considered as coming from embryonal rests, sudoriferous glands, basal cells, sebaceous glands, and hair follicles.

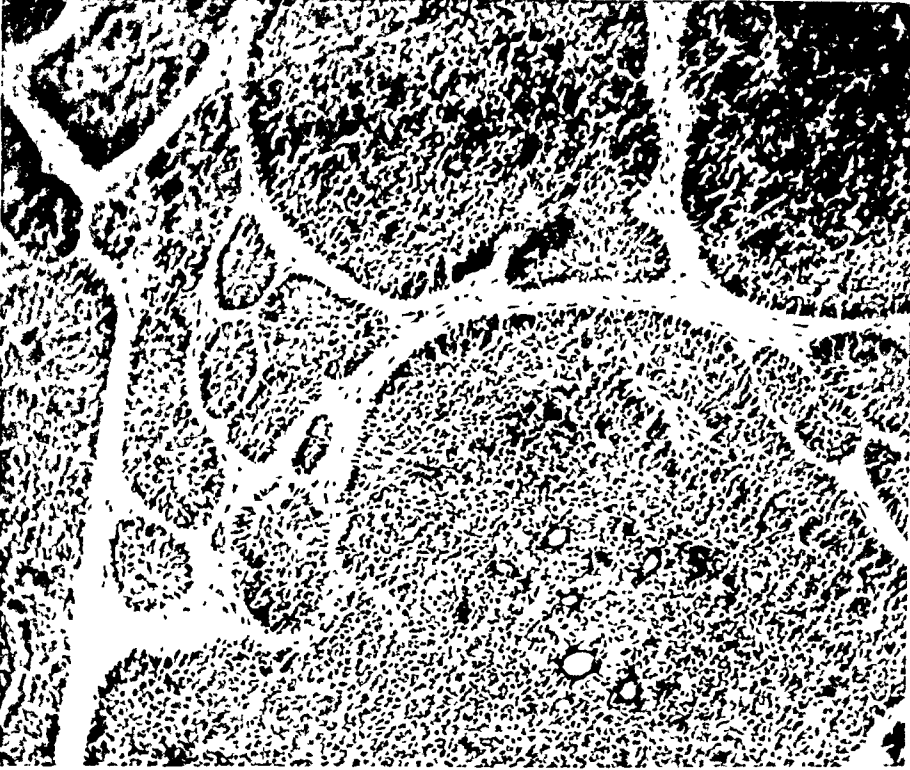
TUMORS OF APOCRINE GLANDS These are rare and do not differ essentially from those described in connection with the eccrines. It seems possible that the hydradenoma papilliferum may in certain instances derive from these, as apocrine glands are usually located in the axillae and groin and on the nipple in the form of Montgomery's tubercles. The frequent occurrence of papillary hydradenoma in the groin and on the

labia may be indicative of some connection of this sort.

Tumors of Ceruminous Glands Ceruminous glands are composed of higher epithelium and one in which there are a pigment and lipid droplets, the secretion is not clear like sweat, but is more like molasses, and it is known as "wax" or "ear wax" after it has become inspissated by exposure to the air in the external auditory meatus where these glands are situated. Nonmalignant tumors traceable to origin in these are decidedly rare, although a very few carcinomas have been described (one of them by Warvi and Gates). The microscopic appearance of such a carcinoma is that of an adenocarcinoma composed of irregular strands or groups of large polyhedral cells with clear cytoplasm containing lipids that may be brightly stained with sudan IV. They also exhibit an iron containing pigment. The tumor is somewhat brownish on gross examination and exhibits little invasive or metastatic propensities.

Tumors Originating in the Corium
XANTHOMA Few of the xanthomas prove to be true tumors on critical examination. They form yellowish growths that may be tuberculous or flat and are apt to accompany hypercholesterolemia, diabetes, and the Hand-Schüller-Christian syndrome. They may be quite firm and are usually well circumscribed. Under the microscope they are seen to be made up of collections of foam cells or Touton cells that form alveolar, solid masses. When such collections appear in the eyelids of elderly subjects they have a flat, spot-like quality and are known as "xanthelasma."

NEVI The vascular nevi are discussed under "Angiomas" in the chapter on the cardiovascular system, while those of the pigmented variety are described under "Tumors of Neural Terminals" in the chapter on the nervous system. A "nevus" is merely a birthmark or congenital tumor or blemish. There are clinical varieties of pigmented tumors, however, that should be briefly noted here.



Typical example of a solid hydradenoma, formerly known as "cylindroma." Note nests of cells and resemblance of the tumor to "hair-matrix" or "basal-celled" carcinoma and the epithelioma adenoides cysticum.



Solid hydradenoma. At left are several typical cellular masses; note that one of them appears to be in direct communication with a coiled sudoriferous duct. At extreme right is the covering epidermis.

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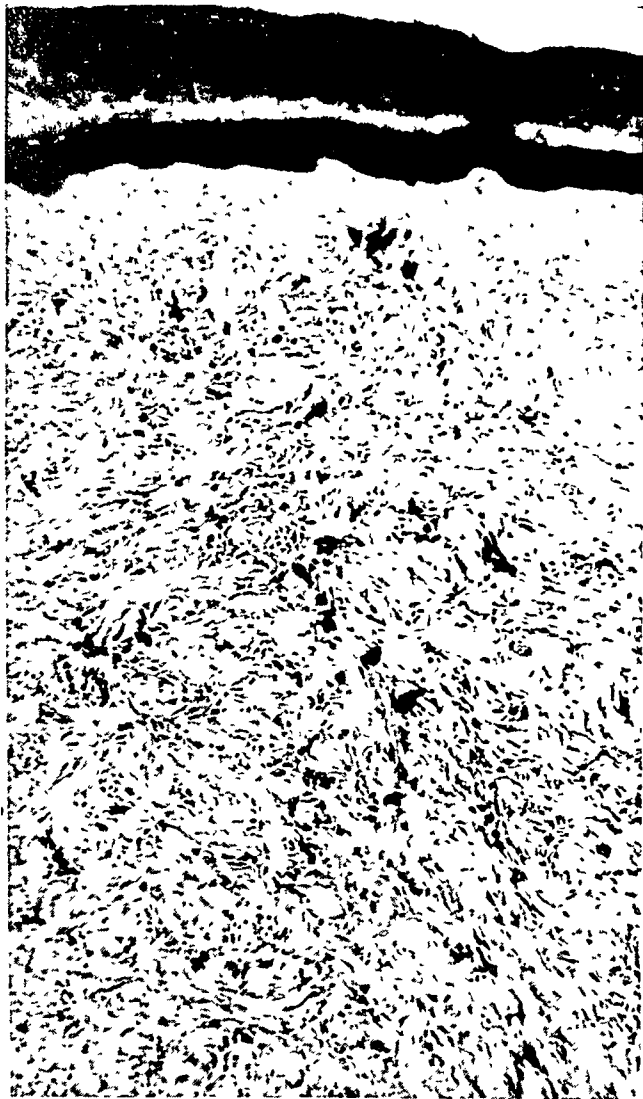
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Mongolian Spot. This is a bluish spot seen in the sacral region of Mongolians and occasionally in Caucasians; it was first described in connection with the Eskimos of Greenland. It represents a small focus of large



Field from a melanophoroma or "blue mole." Pigmented cells are strewn about in a haphazard fashion and do not form "nevus nests," as do those of neurogenic melanotic nevus.

pigmented cells that remain limited, do not proliferate, and are scarcely to be considered as anything more than characteristic blemishes.

Blue Nevus. This resembles the Mongolian spot, but it is a tumor. It is composed of the same large cells, which are so packed with melanin that little can be made out of their histologic characteristics. They may occur anywhere. As they lie deeply situated

in the corium, the intervening tissue changes their brown color to a bluish or violaceous hue. On microscopic examination they are found to be composed of large polygonal, fusiform, or stellate cells that resemble melanophores. When one can be found with sufficiently little pigment to permit examination of the nucleus it is determined to be large and hyperchromatic and distinctly of the "malignant" type. The nature of these cells is still disputed; some believe them to be melanophores and the tumor a melanophoroma, while others (like McCarthy) deny this. When isolated and seen in children they are seldom malignant if widely excised; in adults the prognosis is a tossup. In either case they should be thoroughly removed, and in adults a block dissection of the regional lymph nodes should be carried out if there is yet time. They often metastasize to these nodes.

Melanoma. Pigmented nevi may arise singly, may or may not contain melanin, may be superficial in the epidermal layers (intra-epidermal), or may cause papillary outgrowths that are combined with verruca seborrhoeica. They may cover wide areas, as in the case of the "bathing-trunk nevus." Sometimes they are associated with vascular nevi or small leiomyomas of the skin. Microscopically considered they are equally versatile, varying from orderly nests of "nevus cells" to very diffuse and disorderly masses of such cells strewn over fairly wide areas of the section. They may be predominantly of nervous composition (neuronevi), with many bands of tissue resembling neuroglial elements running among scanty nests of nevus cells.

Finally, these nevi may be malignant and constitute the most dangerous of all tumors, the malignant melanoma. The treatment of these always poses a problem, because they metastasize early and widely by the blood stream as well as by the lymphatics. Hence block dissection of regional lymph nodes is of questionable value, although it should always be done when feasible. It should be noted that hyper-

plastic pigmented nevi in children frequently look much more dangerous than they are, and that a wide excision will usually eliminate them. It is equally important to stress the point that the slightest evidence of ma-



"Leukemia cutis" in lymphogenous leukemia. Corium is densely infiltrated by immature lymphoid cells which constitute a broad zone just beneath epidermis. This is to be differentiated from mycosis fungoides, which has many similarities.

lignant change in a pigmented tumor in the case of an adult should call for drastic surgery. Treatment with the x-ray or with radium has proved to be of little or no value, as is the case with neurogenous tumors in general. Melanoma has been more fully described in Chapter 20.

LEIOMYOMA CUTIS. There are small tumors of smooth muscle that develop either

as multiple and painless nodules just beneath the skin or as solitary and often distressingly painful masses in this situation. They arise in the arrectores pilorum, the small muscles that erect the hair shafts during fright, chilliness, or other such nervous phenomena. There is not much to be said about them aside from the fact that they are much like any other leiomyomas and that the reason why the solitary examples should be painful is most obscure. These are often confused with glomus tumors and are removed under that mistaken impression. Stout has written a very good article on the subject.

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